

09763499

FILE 'HOME' ENTERED AT 12:12:49 ON 20 SEP 2008

=>

=> FIL REGISTRY

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 12:13:14 ON 20 SEP 2008

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2008 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 SEP 2008 HIGHEST RN 1050750-61-2

DICTIONARY FILE UPDATES: 19 SEP 2008 HIGHEST RN 1050750-61-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=> s triclosan

L1 5 TRICLOSAN

=> d l1 1-5

L1 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2008 ACS on STN

RN 756493-59-1 REGISTRY

ED Entered STN: 04 Oct 2004

CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)-, mixt. with ethanol (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Ethanol-triclosan mixt.

MF C12 H7 C13 O2 . C2 H6 O

CI MXS

SR CA

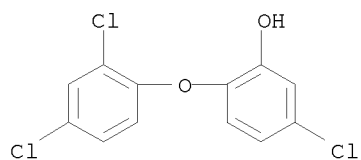
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 3380-34-5

CMF C12 H7 C13 O2

09763499



CM 2

CRN 64-17-5
CMF C2 H6 O

H₃C—CH₂—OH

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2008 ACS on STN
RN 756493-58-0 REGISTRY
ED Entered STN: 04 Oct 2004
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)-, mixt. with 2-propanol (9CI)
(CA INDEX NAME)

OTHER NAMES:

CN Isopropanol-triclosan mixt.

MF C12 H7 Cl3 O2 . C3 H8 O

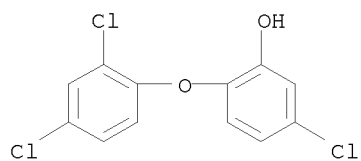
CI MXS

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

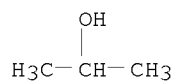
CM 1

CRN 3380-34-5
CMF C12 H7 Cl3 O2



CM 2

CRN 67-63-0
CMF C3 H8 O



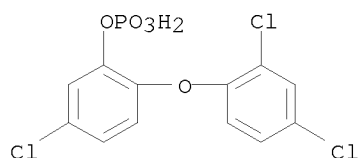
1 REFERENCES IN FILE CA (1907 TO DATE)

Jagoe

09763499

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

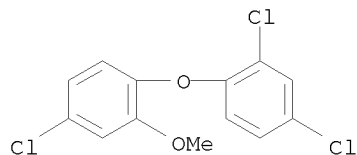
L1 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2008 ACS on STN
RN 67651-57-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)-, 1-(dihydrogen phosphate) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)-, dihydrogen phosphate (9CI)
OTHER NAMES:
CN Triclosan monophosphate
DR 163886-25-7
MF C12 H8 Cl3 O5 P
LC STN Files: BIOSIS, CA, CAPLUS, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

22 REFERENCES IN FILE CA (1907 TO DATE)
22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2008 ACS on STN
RN 4640-01-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Benzene, 4-chloro-1-(2,4-dichlorophenoxy)-2-methoxy- (CA INDEX NAME)
OTHER NAMES:
CN 2,4,4'-Trichloro-2'-methoxydiphenyl ether
CN 5-Chloro-2-(2,4-dichlorophenoxy)anisole
CN Methyl triclosan
CN Triclosan methyl
MF C13 H9 Cl3 O2
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CSNB, TOXCENTER, USPATFULL, USPATOLD
(*File contains numerically searchable property data)



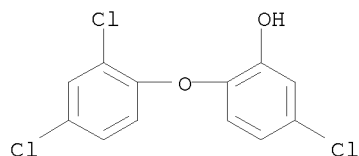
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

37 REFERENCES IN FILE CA (1907 TO DATE)
38 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L1 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2008 ACS on STN
RN 3380-34-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)- (CA INDEX NAME)
OTHER NAMES:
CN 2',4',4'-Trichloro-2-hydroxydiphenyl ether
CN 2',4,4'-Trichloro-2-hydroxydiphenyl ether
CN 2'-Hydroxy-2,4,4'-trichlorodiphenyl ether
CN 2,2'-Oxybis(1',5'-dichlorophenyl-5-chlorophenol)
CN 2,4,4'-Trichloro-2'-hydroxydiphenyl ether
CN 2-Hydroxy-2',4,4'-trichlorodiphenyl ether
CN 3-Chloro-6-(2,4-dichlorophenoxy)phenol
CN 4-Chloro-2-hydroxyphenyl 2,4-dichlorophenyl ether
CN 5-Chloro-2-(2,4-dichlorophenoxy)phenol
CN Aquasept
CN Bacti-Stat soap
CN Cansan TCH
CN CH 3565
CN CH 3635
CN DP 300
CN Gamophen
CN Irgacare MP
CN Irgacide LP 10
CN Irgaguard B 1000
CN Irgaguard B 1325
CN Irgasan
CN Irgasan CH 3565
CN Irgasan DP 30
CN Irgasan DP 300
CN Irgasan DP 3000
CN Irgasan DP 400
CN Irgasan PE 30
CN Irgasan PG 60
CN Microban Additive B
CN Microban B
CN NM 100
CN Olettron
CN Sanitized XTX
CN Sapoderm
CN SterZac
CN TCCP
CN THDP
CN Tinosan AM 100
CN Tinosan AM 110
CN Triclosan
CN Ultra Fresh NM 100
CN Ultrafresh NM-V 2
CN Vinyzene DP 7000
CN Yujiexin
CN Zilesan UW
DR 164325-69-3, 112099-35-1, 88032-08-0, 261921-78-2
MF C12 H7 C13 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
CHEMLIST, CIN, CSChem, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT,
IFIUDB, IMSDRUGNEWS, IMSPRODUCT, IPA, MEDLINE, MRCK*, MSDS-OHS, PIRA,
PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2,
USPATFULL, USPATOLD, VETU

09763499

(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3343 REFERENCES IN FILE CA (1907 TO DATE)
63 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3357 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> FIL MEDICINE

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

16.53

16.74

FILE 'ADISCTI' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 Adis Data Information BV

FILE 'ADISINSIGHT' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 Adis Data Information BV

FILE 'ADISNEWS' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 Adis Data Information BV

FILE 'BIOSIS' ENTERED AT 12:14:55 ON 20 SEP 2008

Copyright (c) 2008 The Thomson Corporation

FILE 'BIOTECHNO' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'CAPLUS' ENTERED AT 12:14:55 ON 20 SEP 2008

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'DDFB' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 THOMSON REUTERS

FILE 'DDFU' ACCESS NOT AUTHORIZED

FILE 'DGENE' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 THOMSON REUTERS

FILE 'DISSABS' ENTERED AT 12:14:55 ON 20 SEP 2008

COPYRIGHT (C) 2008 ProQuest Information and Learning Company; All Rights Reserved.

FILE 'DRUGB' ENTERED AT 12:14:55 ON 20 SEP 2008

Jagoe

09763499

COPYRIGHT (C) 2008 THOMSON REUTERS

FILE 'DRUGMONOG2' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 IMSWORLD Publications Ltd

FILE 'DRUGU' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 THOMSON REUTERS

FILE 'EMBAL' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright (c) 2008 Elsevier B.V. All rights reserved.

FILE 'EMBASE' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright (c) 2008 Elsevier B.V. All rights reserved.

FILE 'ESBIOBASE' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'IFIPAT' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 IFI CLAIMS(R) Patent Services (IFI)

FILE 'IMSDRUGNEWS' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 IMSWORLD Publications Ltd

FILE 'IMSPRODUCT' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 IMSWORLD Publications Ltd

FILE 'IPA' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright (c) 2008 The Thomson Corporation

FILE 'KOSMET' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 International Federation of the Societies of Cosmetics Chemists

FILE 'LIFESCI' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Cambridge Scientific Abstracts (CSA)

FILE 'MEDLINE' ENTERED AT 12:14:55 ON 20 SEP 2008

FILE 'NAPRALERT' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Board of Trustees of the University of Illinois,
University of Illinois at Chicago.

FILE 'NLDB' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Gale Group. All rights reserved.

FILE 'NUTRACEUT' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright 2008 (c) MARKETLETTER Publications Ltd. All rights reserved.

FILE 'PASCAL' ENTERED AT 12:14:55 ON 20 SEP 2008
Any reproduction or dissemination in part or in full,
by means of any process and on any support whatsoever
is prohibited without the prior written agreement of INIST-CNRS.
COPYRIGHT (C) 2008 INIST-CNRS. All rights reserved.

FILE 'PCTGEN' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 WIPO

FILE 'PHARMAML' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright 2008 (c) MARKETLETTER Publications Ltd. All rights reserved.

09763499

FILE 'PHIC' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Informa UK Ltd.

FILE 'PHIN' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 Informa UK Ltd.

FILE 'SCISEARCH' ENTERED AT 12:14:55 ON 20 SEP 2008
Copyright (c) 2008 The Thomson Corporation

FILE 'TOXCENTER' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USGENE' ENTERED AT 12:14:55 ON 20 SEP 2008
COPYRIGHT (C) 2008 SEQUENCEBASE CORP

FILE 'USPATFULL' ENTERED AT 12:14:55 ON 20 SEP 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATOLD' ENTERED AT 12:14:55 ON 20 SEP 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 12:14:55 ON 20 SEP 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l1
L2 13207 L1

=> s triclosan
L3 19219 TRICLOSAN

=> s l2 or l3
L4 21003 L2 OR L3

=> s malaria?
L5 357840 MALARIA?

=> s antimalaria?
L6 124642 ANTIMALARIA?

=> s l5 or l6
L7 408372 L5 OR L6

=> s l4 and l7
L8 474 L4 AND L7

=> s falciparum or berghei
L9 207454 FALCIPARUM OR BERGHEI

=> s l8 and l9
L10 312 L8 AND L9

=> s l10 an dl9
MISSING OPERATOR L10 AN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l9 an dl10
MISSING OPERATOR L9 AN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

Jagoe

09763499

=> d his

(FILE 'HOME' ENTERED AT 12:12:49 ON 20 SEP 2008)

FILE 'REGISTRY' ENTERED AT 12:13:14 ON 20 SEP 2008

L1 5 S TRICLOSAN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CAPLUS, DDFB, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIODBASE, IFIPAT, IMSDRUGNEWS, IMSPRODUCT, IPA, KOSMET, LIFESCI, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, PHARMAML, ...' ENTERED AT 12:14:55 ON 20 SEP 2008

L2 13207 S L1
L3 19219 S TRICLOSAN
L4 21003 S L2 OR L3
L5 357840 S MALARIA?
L6 124642 S ANTIMALARIA?
L7 408372 S L5 OR L6
L8 474 S L4 AND L7
L9 207454 S FALCIPARUM OR BERGHEI
L10 312 S L8 AND L9

=> s triclosan/ab

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L11 6149 TRICLOSAN/AB

=> s l10 and l11

L12 166 L10 AND L11

=> s quinine or atabrine or chloroquine or mefloquine or primaquine or artemisinin or artemether or artesunate

L13 217939 QUININE OR ATABRINE OR CHLOROQUINE OR MEFLUQUINE OR PRIMAQUINE
OR ARTEMISININ OR ARTEMETHER OR ARTESUNATE

=> s l12 and l13

L14 22 L12 AND L13

=> dup rem

Jagoe

09763499

ENTER L# LIST OR (END):122

L22 IS NOT VALID HERE

The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> dup rem

ENTER L# LIST OR (END):114

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2, IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

PROCESSING COMPLETED FOR L14

L15 11 DUP REM L14 (11 DUPLICATES REMOVED)

=> d 115 1-11 ibib, kwic

L15 ANSWER 1 OF 11 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 1

ACCESSION NUMBER: 2007:278443 BIOSIS

DOCUMENT NUMBER: PREV200700251712

TITLE: Antiplasmodial interactions between artemisinin and triclosan or ketoconazole combinations against blood stages of Plasmodium falciparum in vitro.

AUTHOR(S): Mishra, Lokesh C.; Bhattacharya, Amit; Bhasin, Virendra K.
[Reprint Author]

CORPORATE SOURCE: Univ Delhi, Dept Zool, N Campus Delhi Univ, Delhi 110007, India
virendrabhasin@hotmail.com

SOURCE: American Journal of Tropical Medicine and Hygiene, (MAR 2007) Vol. 76, No. 3, pp. 497-501.
CODEN: AJTHAB. ISSN: 0002-9637.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 25 Apr 2007

Last Updated on STN: 24 Oct 2007

TI Antiplasmodial interactions between artemisinin and triclosan or ketoconazole combinations against blood stages of Plasmodium falciparum in vitro.

AB Emergence of drug-resistant Plasmodium falciparum strains to conventional first-line antimalarial drugs has compelled many countries to reorient their drug policies to adopt artemisinin-based combination therapies (ACTs) for treatment of uncomplicated malaria. This has increased the demand of artemisinin, already a scarce commodity. Synthesis of artemisinin is not yet commercially viable. Extensive use of available ACTs will invariably lead to emergence of resistance to these combinations. Thus, there is need to search for new artemisinin-based synthetic, inexpensive, synergistic combinations to reduce dependence on artemisinin. In vitro cultures of P. falciparum provide an appropriate system for identification of such new combinations. We evaluated interactions of artemisinin with triclosan or ketoconazole against blood stages of P. falciparum by a fixed-ratio isobologram method. Artemisinin shows mild synergistic interaction with triclosan and slight to marked antagonism with ketoconazole in vitro. These antiplasmodial interactions, however, require confirmation using in vivo model systems.

IT

. . .
Pharmacology; Parasitology; Hematology (Human Medicine, Medical Sciences)

09763499

IT Parts, Structures, & Systems of Organisms
 blood: blood and lymphatics
IT Diseases
 malaria: blood and lymphatic disease, infectious disease,
 parasitic disease, drug therapy
 Malaria (MeSH)
IT Chemicals & Biochemicals
 artemisinin: antiinfective-drug, antiparasitic-drug;
 ketoconazole: antiinfective-drug, antifungal-drug; triclosan:
 antiinfective-drug, antiseptic/disinfectant-drug

ORGN . . .

Taxa Notes

 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier

 Sporozoa 35400

Super Taxa

 Protozoa; Invertebrata; Animalia

Organism Name

 Plasmodium falciparum (species): parasite, strain-3D7

Taxa Notes

 Animals, Invertebrates, Microorganisms, Protozoans

RN 63968-64-9 (artemisinin)

65277-42-1 (ketoconazole)

3380-34-5 (triclosan)

L15 ANSWER 2 OF 11 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights
reserved on STN

ACCESSION NUMBER: 2007126774 EMBASE

TITLE: Enoyl reductases as targets for the development of
anti-tubercular and anti-malarial agents.

AUTHOR: Oliveira, J.S.; Vasconcelos, I.B.; Santos, Diogenes S.
(correspondence); Basso, Luiz A.

CORPORATE SOURCE: Centro de Pesquisas em Biologia Molecular e Funcional,
Faculdade de Biociencias, Pontificia Universidade Catolica
do Rio Grande do Sul, Porto Alegre, RS, Brazil. luiz.basso@
pucrs.br; diogenes@pucrs.br

AUTHOR: Moreira, I.S.

CORPORATE SOURCE: Departamento de Quimica Organica e Inorganica, Universidade
Federal do Ceara, Fortaleza, CE, Brazil.

AUTHOR: Santos, Diogenes S. (correspondence)

CORPORATE SOURCE: Centro de Pesquisas em Biologia Molecular e Funcional,
Faculdade de Biociencias, Pontificia Universidade Catolica
do Rio Grande do Sul, Porto Alegre, RS, Brazil. diogenes@pu
crs.br

SOURCE: Current Drug Targets, (Mar 2007) Vol. 8, No. 3, pp.
399-411.

Refs: 139

ISSN: 1389-4501 CODEN: CDTUAA

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review; (Review)

FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology

030 Clinical and Experimental Pharmacology

036 Health Policy, Economics and Management

037 Drug Literature Index

038 Adverse Reactions Titles

004 Microbiology: Bacteriology, Mycology, Parasitology
and Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 17 Apr 2007

Jagoe

Last Updated on STN: 17 Apr 2007

- TI Enoyl reductases as targets for the development of anti-tubercular and anti-malarial agents.
- AB Tuberculosis (TB) and Malaria are neglected diseases, which continue to be major causes of morbidity and mortality worldwide, killing together around 5 million people. . . the Type II fatty acid biosynthesis system, which elongates acyl fatty acid precursors of mycolic acids. M. tuberculosis and P. falciparum enoyl reductases are targets for the development of anti-tubercular and antimalarial agents. Here we present a brief description of the mechanism of action of, and resistance to, isoniazid. In addition, data on inhibition of mycobacterial and plasmodial enoyl reductases by triclosan are presented. We also describe recent efforts to develop inhibitors of M. tuberculosis and P. falciparum enoyl reductase enzyme activity. .COPYRGT. 2007 Bentham Science Publishers Ltd.
- CT Medical Descriptors:
- antibiotic resistance
 - chemical analysis
 - combination chemotherapy
 - cost of illness
 - drug mechanism
 - drug metabolism
 - drug structure
 - drug targeting
 - enzyme inhibition
 - fatty acid synthesis
 - genetic analysis
 - human
 - malaria: DM, disease management
 - malaria: DR, drug resistance
 - malaria: DT, drug therapy
 - malaria: EP, epidemiology
 - molecular weight
 - morbidity
 - mortality
 - Mycobacterium
 - Mycobacterium tuberculosis
 - nonhuman
 - Plasmodium falciparum
 - prescription
 - product development
 - review
 - structural gene
 - tuberculosis: DM, disease management
 - tuberculosis: DR, drug resistance
 - tuberculosis: DT, drug therapy
 - tuberculosis: EP, epidemiology
 - unspecified side effect: SI, side effect
 - amikacin: DT, drug therapy
 - aminosalicylic acid: DT, drug therapy
 - amodiaquine: AN, drug analysis
 - amodiaquine: CB, drug combination
 - amodiaquine: DT, drug therapy
 - *antimalarial agent: AE, adverse drug reaction
 - *antimalarial agent: DV, drug development
 - artemisinin: AN, drug analysis
 - artemisinin: CM, drug comparison
 - artemisinin: DT, drug therapy
 - artemisinin: PE, pharmacoeconomics
 - artesunate: AN, drug analysis

artesunate: CB, drug combination
artesunate: DT, drug therapy
chloroquine: AN, drug analysis
chloroquine: CB, drug combination
chloroquine: CM, drug comparison
chloroquine: DT, drug therapy
chloroquine: PE, pharmacoeconomics
 cycloserine: DT, drug therapy
 *enoyl acyl carrier protein reductase (NADH): EC, endogenous compound
 ethambutol: CB, drug combination
 ethambutol: DT, drug therapy
 ethambutol: PD, . . . analysis
 isoniazid: CB, drug combination
 isoniazid: DT, drug therapy
 isoniazid: PK, pharmacokinetics
 isoniazid: PD, pharmacology
 isoniazid derivative: AN, drug analysis
 isoniazid derivative: PD, pharmacology
 kanamycin: DT, drug therapy
mefloquine: AN, drug analysis
mefloquine: CB, drug combination
mefloquine: DT, drug therapy
 mycolic acid: EC, endogenous compound
 oxidoreductase: EC, endogenous compound
 pyrazinamide: CB, drug combination
 pyrazinamide: DT, drug therapy
 pyrazinamide: PD, pharmacology
 pyrimethamine: AN, drug analysis
 pyrimethamine: CB, drug combination
 pyrimethamine: IT, drug interaction
 pyrimethamine: DT, drug therapy
 pyrimethamine: PD, pharmacology
quinine: AN, drug analysis
quinine: DT, drug therapy
 quinoline derived antiinfective agent: DT, drug therapy
 rifampicin: CB, drug combination
 rifampicin: DT, drug therapy
 rifampicin: PD, pharmacology
 streptomycin: CB, drug combination
 streptomycin: . . . drug therapy
 streptomycin: PD, pharmacology
 sulfadoxine: AN, drug analysis
 sulfadoxine: CB, drug combination
 sulfadoxine: IT, drug interaction
 sulfadoxine: DT, drug therapy
 sulfadoxine: PD, pharmacology
 thioester: EC, endogenous compound
triclosan: AN, drug analysis
triclosan: PD, pharmacology
 *tuberculostatic agent: AE, adverse drug reaction
 *tuberculostatic agent: DV, drug development
 unindexed drug
 RN (amikacin) 37517-28-5, 39831-55-5; (aminosalicylic acid) 133-10-8,
 133-15-3, 28088-64-4, 51540-64-8, 65-49-6, 80702-32-5; (amodiaquine)
 69-44-3, 86-42-0; (artemisinin) 63968-64-9; (artesunate)
 82864-68-4, 88495-63-0; (chloroquine) 132-73-0, 3545-67-3,
 50-63-5, 54-05-7; (cycloserine) 339-72-0, 68-39-3, 68-41-7; (enoyl acyl
 carrier protein reductase (NADH)) 37251-08-4; (ethambutol) 10054-05-4,
 1070-11-7, 3577-94-4, 74-55-5; (ethionamide) 536-33-4; (fansidar)
 37338-39-9; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (kanamycin)

11025-66-4, 61230-38-4, 8063-07-8; (mefloquine) 51773-92-3,
 53230-10-7; (mycolic acid) 37281-34-8; (oxidoreductase) 9035-73-8,
 9035-82-9, 9037-80-3, 9055-15-6; (pyrazinamide) 98-96-4; (pyrimethamine)
 53640-38-3, 58-14-0; (quinine) 130-89-2, 130-95-0, 14358-44-2,
 549-48-4, 549-49-5, 60-93-5, 7549-43-1; (rifampicin) 13292-46-1;
 (streptomycin) 57-92-1; (sulfadoxine) 2447-57-6; (triclosan)
 3380-34-5

L15 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2007:40291 CAPLUS

DOCUMENT NUMBER: 146:243322

TITLE: Inhibitors of nonhousekeeping functions of the
 apicoplast defy delayed death in Plasmodium
falciparum

AUTHOR(S): Ramya, T. N. C.; Mishra, Satyendra; Karmodiya,
 Krishanpal; Suroolia, Namita; Suroolia, Avadhesh

CORPORATE SOURCE: Molecular Biophysics Unit, Indian Institute of
 Science, Bangalore, 560012, India

SOURCE: Antimicrobial Agents and Chemotherapy (2007), 51(1),
 307-316

CODEN: AMACQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Inhibitors of nonhousekeeping functions of the apicoplast defy delayed
 death in Plasmodium falciparum

AB . . . demonstrate that antibiotics like clindamycin, chloramphenicol,
 and tetracycline, inhibitors of prokaryotic protein synthesis, invoke the
 delayed death phenotype in Plasmodium falciparum, too, as
 evident from a specific reduction of apicoplast genome copy number
 Interestingly, however, mols. like triclosan, cerulenin, fops,
 and NAS-91, inhibitors of the recently discovered fatty acid synthesis
 pathway, and succinyl acetone, an inhibitor of heme. . . apicoplast as
 the site of metabolic pathways, which are required for parasite survival,
 and thus subserve the development of novel antimalarial therapy.

ST apicoplast inhibitor antimalarial malaria Plasmodium
falciparum

IT Antimalarials

Malaria

Plasmodium falciparum

(inhibitors of nonhousekeeping functions of apicoplast defy delayed
 death in Plasmodium falciparum)

IT 54-05-7, Chloroquine 56-75-7, Chloramphenicol 60-54-8,
Tetracycline 66-81-9, Cycloheximide 111-11-5, Methyl octanoate
 112-39-0, Methyl palmitate 244-54-2, Diphenylene iodonium 1077-27-6,
S-Lipoic acid 1200-22-2 3380-34-5, Triclosan
 12772-57-5, Radicalol 13292-46-1, Rifampin 17397-89-6, Cerulenin
 18323-44-9, Clindamycin 50594-66-6, Acifluorfen 51568-18-4, Succinyl
acetone 69335-91-7, Fluazifop 69806-34-4, Haloxifop 76578-12-6,
Quizalofop 642093-27-4, NAS 91

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(inhibitors of nonhousekeeping functions of apicoplast defy delayed
 death in Plasmodium falciparum)

L15 ANSWER 4 OF 11 DISSABS COPYRIGHT (C) 2008 ProQuest Information and
 Learning Company; All Rights Reserved on STN

ACCESSION NUMBER: 2007:10710 DISSABS Order Number: AAI3221126

TITLE: Development and application of a rapid site-specific integration system in the malaria parasite Plasmodium falciparum

AUTHOR: Nkrumah, Louis John [Ph.D.]; Fidock, David A. [advisor]; Jacobs, William R., Jr. [advisor]

CORPORATE SOURCE: Yeshiva University (0266)

SOURCE: Dissertation Abstracts International, (2006) Vol. 67, No. 6B, p. 2953. Order No.: AAI3221126. 147 pages. ISBN: 978-0-542-74229-3.

DOCUMENT TYPE: Dissertation

FILE SEGMENT: DAI

LANGUAGE: English

ENTRY DATE: Entered STN: 20070226
Last Updated on STN: 20070226

TI Development and application of a rapid site-specific integration system in the malaria parasite Plasmodium falciparum

AB The current transfection techniques for genomic integration and complementation studies in the malaria parasite, Plasmodium falciparum, are inefficient and labor-intensive. It takes 3-5 months to achieve genetic integration in the parasite, many of which result in. . . integration of the plasmid into undesired regions of the genome. We have developed an efficient, site-specific integration system in P. falciparum, which uses the Bxb1 mycobacteriophage integrase to rapidly catalyze recombination between an attP plasmid and a chromosomal attB site. Transfection of attB+ P. falciparum lines with the attP plasmid produced recombinant attB x attP parasites within 2-4 weeks. The integration was stable in the. . . compartments in the parasite.

We employed the integrase-mediated attB x attP integration system to test whether pfenr (Plasmodium falciparum enoyl-ACP reductase) is the target of the antimalarial agent triclosan. We generated transgenic P. falciparum parasites expressing the A217V mutant of pfenr that was previously reported to cause a 7000-fold decrease in triclosan binding affinity. However, the A217V mutation failed to confer resistance to triclosan in the parasites. Further studies revealed that neither pfenr transcript nor protein was detectable in the asexual stages of the parasite. Targeted disruption of pfenr in P. falciparum produced viable parasites with no growth defects. Our results suggest that pfenr is not essential in the asexual stages of P. falciparum, where triclosan has been reported to kill the parasites, and hence may not be the target of triclosan.

We used allelic exchange technique to investigate the role of PfnHE (P. falciparum sodium-proton exchanger) in quinine resistance. Replacing the endogenous 3' untranslated region (UTR) of pfnhe with a truncated 3'UTR resulted in under-expression of PfnHE and a subsequent 30% reduction in quinine resistance in recombinant P. falciparum clones. The decrease in quinine resistance was observed only in parasites that were already resistant to quinine, suggesting that PfnHE contributes to quinine resistance, but only in a genome context already conferring a basal level of quinine resistance.

L15 ANSWER 5 OF 11 USPATFULL on STN

ACCESSION NUMBER: 2005:164780 USPATFULL

TITLE: Triclosan dosage form

INVENTOR(S): Lotter, Antonie Philippus, Potchefstroom, SOUTH AFRICA
Du Preez, Jan Lourens, Potchefstroom, SOUTH AFRICA
Collins, Lindi-May, Potchefstroom, SOUTH AFRICA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20050142204	A1	20050630
APPLICATION INFO.:	US 2003-489732	A1	20020918 (10)
	WO 2002-ZA145		20020918

	NUMBER	DATE
PRIORITY INFORMATION:	ZA 2001-7414	20010918
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, 901 NEW YORK AVENUE, NW, WASHINGTON, DC, 20001-4413, US	
NUMBER OF CLAIMS:	18	
EXEMPLARY CLAIM:	1-35	
LINE COUNT:	421	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Triclosan dosage form

AB This invention relates to triclosan and more particularly to a dosage form of triclosan especially for use in the treatment, including prophylaxis, of malaria. This invention further relates to use of a triclosan emulsion or oil solution in the preparation of a composition for use in the treatment, including prophylaxis, of malaria. This invention also relates to a method of treating, including prophylaxis of malaria and the use of a triclosan emulsion or oil solution in such a method.

SUMM This invention relates to triclosan and more particularly to a dosage form of triclosan especially for use in the treatment, including prophylaxis, of malaria. This invention further relates to use of triclosan in the preparation of a composition for use in the treatment, including prophylaxis, of malaria. This invention also relates to a method of treating, including prophylaxis, of malaria and the use of triclosan in such a method.

SUMM Malaria remains a leading global health problem, despite considerable efforts to control the disease over several decades. Approximately 40% of the world's population live in malaria-endemic areas, with about 90% of cases and most deaths occurring in tropical Africa (Beeson et al., 2001:149). There are up. . . of which 1 million are child fatalities annually (WB, 2001). the majority of severe clinical disease is due to Plasmodium falciparum, the young children and pregnant women at highest risk (Beeson, et al., 2001:149).

SUMM Malaria also has a significant negative economic effect. Research shows that malaria-afflicted families are able to harvest only approximately 40% of their crops, compared with healthy families, suggesting a link between malaria and poverty. The direct and indirect costs of malaria in Africa alone are estimated to exceed US \$2 billion per year, while it is believed that the disease could be controlled with a budget amounting to one-tenth of this amount. Malaria slows economic growth in African countries by an estimated 1.3% each year (MRC, 2001).

SUMM Malaria is caused by several species of the protozoan Plasmodium, of which P. vivax and P. falciparum are the most common. They all have complex life cycles involving both the Anopheles mosquito and the erythrocyte of the. . . host. In vivax, a persisting tissue phase continues to infect the blood at intervals for many years. Thus, the ideal antimalarial should not only eradicate the microzoan from the blood, (i.e., to `suppress` the clinical attack) but from the tissues as well, to effect a "radical cure". The several

antimalarials differ in their point of interruption of the cycle of the parasite and in the type of malaria affected (Harvey, 1975:1154).

SUMM Antimalarial treatment has advanced considerably over the last four centuries. Cinchona imported from Peru in 1643 allowed European countries and their colonies some means of suppressing the disease, and the introduction of quinine in the 19th century, followed by pamaquine in 1926 and quinacrine (alabrine) in 1930, improved treatment somewhat (Harvey, 1975:1154).

SUMM When supplies of quinine were cut off in World War II, the US Office of Scientific Research and Development co-ordinated a study of about. . . old, synthetic compounds. Not only were the older German compounds "rediscovered", but also several new and superior agents (including amodiaquine, chloroquine, pentaquine, and primaquine) (Harvey, 1975:1154).

SUMM However, a major problem and disadvantage of the know drugs is the emergence and spread of antimalarial drug resistance. This makes the development of new drugs an important priority (Beeson et al., 2001:149). Resistance of the malaria parasite to chloroquine, one of the cheapest and previously most useful antimalarial agents, is now widespread. Similarly, resistance to the combination of sulphadoxine-pyrimethamine is extensive in Asia and growing in Africa. Resistance. . . in treatment of severe disease, is becoming a major problem in certain parts of Asia. Relatively newer drugs, such as mefloquine, halofantrine, atovaquone-proguanil and artemether-lumefantrine still show efficacy but have limitations such as high cost. Novel uses for old drugs, such as chlorguanil-dapsone, and artemisinin combination therapy offer definite possibilities for the near future, but still have regulatory, policy and implementation hurdles to jump (Beeson. . .

SUMM Triclosan is a well known broad spectrum antibacterial agent active against many organisms. It has been in use as an antimicrobial. . . been done, and it was proven to be safe topically as well as orally (Bhargava, H. & Leonard, P. A., Triclosan: Application and safety, American Journal of Infection Control, vol. 24, no. 3, June 1996).

SUMM Surolia (Surolia, N & Surolia A, Nature Medicine, vol. 7, no. 2 February 2001, p 167-173) showed that triclosan is active against malaria parasites. However, they state that it would be a long time before an oral dosage form is developed. It has. . . Beeson et al. (Beeson, J. G., Winstanely, P. A., McFadden, G. I. & Brown, G. V. New agents to combat malaria. Nature Medicine, vol. 7, no. 2 February 2001, p. 149-150) states that a lot of work is still to be done before the product will be of use. A major disadvantage of triclosan is its very low solubility in water which has a detrimental influence on its absorption and thus its bioavailability. Although extensive toxicity studies have been done, and triclosan has been proven safe for oral use, it has not yet been formulated for this route.

SUMM It is therefore an object of the present invention to provide a dosage form of triclosan especially for the treatment, including prophylactic treatment, of malaria with which the aforesaid problems and disadvantages can be overcome or at least alleviated. Further objects of the invention are to provide use of triclosan in the preparation of a composition for use in the treatment, including prophylaxis, of malaria, a method of treating, including prophylaxis, of malaria and the use of triclosan in such a method, with which the aforesaid problems and disadvantages can be overcome or at least alleviated.

SUMM According to the present invention there is provided use of a

triclosan oil solution and/or triclosan emulsion in the preparation of a composition for use in the treatment, including prophylaxis, of malaria.

SUMM According to another aspect of the present invention there is provided a triclosan oil solution and/or triclosan emulsion for use in the treatment, including prophylaxis, of malaria.

SUMM According to yet another aspect of the present invention there is provided an anti-malaria dosage form comprising a triclosan oil solution and/or triclosan emulsion.

SUMM According to yet another aspect of the present invention there is provided the use of a triclosan oil solution and/or triclosan emulsion in the treatment, including prophylaxis, of malaria.

SUMM According to yet another aspect of the invention there is provided a method of manufacturing an anti-malaria dosage form including the steps of encapsulating triclosan in a form selected from the group consisting of an emulsion and an oil solution.

SUMM The triclosan may be dissolved or emulsified prior to encapsulation in a pharmacological acceptable oil selected from the group consisting of non-mineral. . . .

SUMM The method may include the step of adding prior to encapsulation to the said triclosan form other formulation agents selected from the group consisting of anti-oxidants, BHA, surfactants, emulsifiers, preservatives, masking agents, sweeteners and combinations. . . .

SUMM . . . to yet another aspect of the present invention there is provided a method of treating a human or animal against malaria by administering a triclosan oil solution and/or emulsion to the human or animal. The treatment may also include prophylactic treatment.

SUMM In one embodiment of the invention the triclosan is provided in the form of a triclosan oil solution. The triclosan may be dissolved in any suitable pharmacological acceptable oil, preferably a non-mineral oil. The non-mineral oil may comprise an animal. . . .

SUMM In another embodiment of the invention the triclosan may be provided in the form of a triclosan emulsion. Any suitable triclosan emulsion may be used. In one embodiment of the invention the emulsion comprises an oil-in-water emulsion. The oil may comprise. . . .

SUMM The triclosan oil solution and/or emulsion may be encapsulated, and this is especially the case where the triclosan is dissolved in a pharmacological acceptable oil. It appears that triclosan is very soluble in oils but has a bad taste at high concentration. The oily solution of triclosan may therefore not be acceptable to patients when administered as such and encapsulation should solve this problem. Preliminary studies have also shown that triclosan emulsions have a bad taste and that encapsulation of the emulsion may also be considered. The composition may be microencapsulated. . . .

SUMM The triclosan oil solution and/or emulsion may be taken orally and in such a case the dosage form preferably comprises an encapsulated triclosan oil solution and/or emulsion. It is believed that when administered orally especially as capsules, the triclosan oil solution and/or emulsion may be effectively absorbed via the lymph system.

SUMM The triclosan oil solution and/or suspension may also include other formulation agents. For example in the case where an oil is used. . . . a solvent an anti-oxidant like BHA may be used to prevent oxidation of the oil. In the case of the triclosan suspension, surfactants, which serve as emulsifiers may be used. Preservatives and

masking agents such as sweeteners may also be employed.

DETD Triclosan Oil Solution for Encapsulation

DETD Triclosan in the amount of 100 g was mixed with 200 g of sunflower oil with slight heating (up to 60° C.) until it dissolved. The solution was left to cool and de-aerate. Soft gelatin capsules of the triclosan oil solution were then prepared.

DETD Triclosan Emulsion

DETD The following compounds were used to prepare a high concentration triclosan emulsion:

<u>Triclosan</u>	16 g
Sunflower oil	34 g
BHA	0.01 g
Span 80	5 g
Tween 80	5 g
Methyl paraben	0.1 . . .

DETD The triclosan was weighed and dissolved in the sunflower oil while stirring over low heat (up to 60° C.). When all the triclosan had dissolved, the BHA, Span 80, Tween 90 and preservatives were added. Na-saccharin was dissolved in a little warm water.. . .

DETD The Assessment of the Bioavailability of Triclosan Dosage Forms

DETD HPLC Method for the Determination of Triclosan in Blood

DETD . . .

Injection volume: 100 µl.

Detection: UV at 210 nm.

Retention time: Approximately 5.1 and 6.3 minutes for triclosan and acenaphthene respectively.

Solvent: methanol.

DETD D) Standard Solution:

1. Weigh approximately 20 mg of triclosan accurately and dissolve in 250 ml of solvent.

2. Make further dilutions of 5 ml to 100 ml and. . .

DETD Surolia and Surolia (2001:168) state that 3 µM (580 ng/ml) triclosan is sufficient for 50% inhibition of fatty acid synthesis in *Plasmodium falciparum*. One must assume that this includes triclosan in both the conjugated and unconjugated form.

DETD Results and Discussion

TABLE 1

Total triclosan in Plasma

	subject no.				
	1	2	3	4	Mean
Time (hours)	ng/ml				

0	0	0	0	0	0
---	---	---	---	---	---

0.333	248	1468	1622	1218.	. . .
-------	-----	------	------	-------	-------

DETD As can be seen from tables 1 and 2 as well as FIG. 1, triclosan was released from the soft gelatine capsules and absorbed. The bioavailability was good in three of the four volunteers. The. . .

DETD Triclosan concentrations as high as 22000 ng/ml (22 µg/ml) was found in plasma, which is about 30 times higher than the. . .

DETD The applicant has therefore found that triclosan in the form of any emulsion or an oil solution is an effective composition and dosage form for the treatment, including prophylaxis, of malaria

. However, it will be appreciated that many variations in detail are possible with a dosage form of triclosan, the use of triclosan, a method of treating malaria according to the invention without departing from the scope of the appended claims. For example, the triclosan could be dissolved or emulsified in a pharmacological acceptable oil selected from the group consisting of non-mineral oils, animal derived. . . oils, plant derived oils, sunflower oil, olive oil, arachis oil, and sesame oil, and mixtures thereof. Further for example, the triclosan form could include other formulation agents selected from the group consisting of anti-oxidants, BHA, surfactants, emulsifiers, preservatives, masking agents, sweeteners and combinations thereof. Even further for example, the triclosan form could be encapsulated or microencapsulated. Yet further for example, the triclosan form could be prepared in the form of soft gelatin capsules.

DETD 1. BEESON, J. G., WINSTANLEY, P. A., MCFADDEN, G. I. & BROWN, G. V. 2001. New agents to combat malaria. Nature medicine 7(2):149-150, February.

DETD 3. MRC (Medical Research Council, South Africa). 2001. General information on malaria. Available on Internet: http://www.malaria.org.za/Malaria_Risk/General_Information/general_information.htm

DETD 5. SCHULZE, J., MARQUARDT, F., LYMAN, F. & SPITZER, C. 1974. Determination of free and conjugated triclosan in blood by electron capture gas liquid chromatography. Journal of the American Oil Chemists' Society, 52:215-218.

DETD 6. SUROLIA, N. AND SUROLIA, A. 2001. Triclosan offers protection against blood stages of malaria by inhibiting enoyl-ACP reductase of Plasmodium falciparum. Nature medicine, 7(2):167-173, February.

DETD 7. WB (World Bank). 2001. Malaria at a glance. Available on Internet: <http://www.rbm.who.int> [Date of use: Aug. 24, 2001].

CLM What is claimed is:

36. A method of manufacturing an oral anti-malaria dosage form including the steps of encapsulating triclosan in a form selected from the group consisting of an emulsion and an oil solution.

CLM What is claimed is:

37. A method according to claim 36 wherein the triclosan is dissolved or emulsified prior to encapsulation in a pharmacological acceptable oil selected from the group consisting of non-mineral oils, . . .

CLM What is claimed is:

. . . A method according to claim 36 or claim 37 including the step of adding prior to encapsulation to the said triclosan form other formulation agents selected from the group consisting of anti-oxidants, BHA, surfactants, emulsifiers, preservatives, masking agents, sweeteners and combinations. . .

CLM What is claimed is:

39. Triclosan in an encapsulated dosage form selected from the group consisting of an emulsion and an oil solution for use in the oral treatment, including prophylaxis, of malaria.

CLM What is claimed is:

40. Triclosan according to claim 39 which is dissolved or emulsified in a pharmacological acceptable oil selected from the group consisting of. . .

CLM What is claimed is:

41. Triclosan according to claim 39 or claim 40 in combination with formulation agents selected from the group consisting of

- anti-oxidants, BHA,. . .
- CLM What is claimed is:
42. Triclosan according to claim 39 which is microencapsulated.
- CLM What is claimed is:
43. Triclosan according to claim 39 which is prepared as soft gelatin capsules.
- CLM What is claimed is:
44. An anti-malaria oral dosage form comprising triclosan in a form selected from the group consisting of an emulsion and an oil solution in a pharmaceutically acceptable encapsulation. . .
- CLM What is claimed is:
45. An anti-malaria oral dosage form according to claim 44 wherein the triclosan is dissolved or emulsified in a pharmacological acceptable oil selected from the group consisting of non-mineral oils, animal derived oils,. . .
- CLM What is claimed is:
46. An anti-malaria dosage form according to claim 44 or claim 45 wherein the said triclosan form includes other formulation agents selected from the group consisting of anti-oxidants, BHA, surfactants, emulsifiers, preservatives, masking agents, sweeteners and. . .
- CLM What is claimed is:
47. A method of orally treating a human or animal against malaria by administering a pharmaceutically effective amount of triclosan in an oral dosage form selected from the group consisting of an emulsion and an oil solution to the human. . .
- CLM What is claimed is:
48. A method according to claim 47 wherein the triclosan is dissolved or emulsified in a pharmacological acceptable oil selected from the group consisting of non-mineral oils, animal derived oils,. . .
- CLM What is claimed is:
49. A method according to claim 47 or claim 48 wherein the said triclosan form includes other formulation agents selected from the group consisting of anti-oxidants, BHA, surfactants, emulsifiers, preservatives, masking agents, sweeteners and. . .
- CLM What is claimed is:
50. A method according to claim 47 wherein the said triclosan form is microencapsulated.
- CLM What is claimed is:
51. A method according to claim 47 wherein the said triclosan form is prepared as soft gelatin capsules.

IT 3380-34-5, Triclosan
(triclosan dosage forms for malaria treatment)

L15 ANSWER 6 OF 11 USPATFULL on STN
ACCESSION NUMBER: 2004:178280 USPATFULL
TITLE: Fab I and inhibition of apicomplexan parasites
INVENTOR(S): McLeod, Rima, Chicago, IL, UNITED STATES
Muench, Stephen P., Stockport, UNITED KINGDOM
Rafferty, John B., Sheffield, UNITED KINGDOM
Kyle, Dennis E., UNITED STATES
Mui, Ernest J., Chicago, IL, UNITED STATES
Kirisits, Michael J., Chicago, IL, UNITED STATES

Mack, Douglas G., Centennial, CO, UNITED STATES
 Roberts, Craig W., Glasgow, UNITED KINGDOM
 Samuel, Benjamin U., Chicago, IL, UNITED STATES
 Lyons, Russell E., UNITED STATES
 Milhous, Wilbur K., Germantown, MD, UNITED STATES
 Prigge, Sean, Severna Park, MD, UNITED STATES
 Rice, David W., Sheffield, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040137446	A1	20040715
APPLICATION INFO.:	US 2003-465527	A1	20030618 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2001-US49738	20011220
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BARNES & THORNBURG, P.O. BOX 2786, CHICAGO, IL, 60690-2786	
NUMBER OF CLAIMS:	9	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	17 Drawing Page(s)	
LINE COUNT:	764	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Discovery and characterization of an apicomplexan Fab I gene and encoded enzyme and discovery of the triclosan as a lead compound, provide means to rationally design novel inhibitory compositions useful for prevention and treatment of apicomplexan related. . .

SUMM [0001] Discovery and characterization of an apicomplexan Fab I gene and encoded enzyme and the discovery of triclosan as a lead compound, provide means to rationally design novel inhibitory compositions useful for prevention and treatment of apicomplexan and. . .

SUMM [0003] Apicomplexan infections are among the most common and devastating infectious diseases. Malaria (Plasmodium) kills one child every eleven seconds and three million people every year. It is a cause of substantial morbidity. . .

SUMM . . . al., 1998; Waller et al., 1998; Zuther et al., 1999; Payne et al., 2000). Notably, both *T. gondii* and *P. falciparum* have been shown to possess mono-functional, plant- or bacterial-like fatty acid biosynthesis enzymes which are targeted to the plastid organelle. . .

SUMM . . . on the inhibition of ENR by compounds such as the diazaborines (Turnowsky et al., 1989; Baldock et al., 1996) and triclosan (McMurray et al., 1998; Heath et al., 1998; Levy et al., 1999; Payne et al., 2000; and Jones et al., 2000) have validated this enzyme as a target for the development of new antibacterial agents. In particular, triclosan, which is found in many house-hold formulations including soaps, deodorants, hand lotion, toothpaste and impregnated into plastics as an anti-bacterial. . .

SUMM . . . invention relates the first report of apicomplexan Fab I (enoyl acyl carrier protein reductase, ENR) and discloses the effects of triclosan, a potent and specific inhibitor of this enzyme, on the in vitro growth of *T. gondii* and *P. falciparum* chain. A plant-like Fab I in *P. falciparum* was identified by the inventors and the structure was modeled on the *Brassia napus* and *Escherichia coli* structures, alone and complexed to triclosan (5-chloro-2-[2,4 dichloropheoxyl] phenol), which confirmed all the requisite features of an enoyl acyl carrier protein reductase (ENR) and

- its interactions with triclosan. Like the remarkable effect of triclosan on a wide variety of bacteria, this compound markedly inhibits growth and survival of the apicomplexan parasites *P. falciparum* and *Toxoplasma gondii* at low concentrations (i.e., IC₅₀ congruent 150–2000 and 62 nanogram/ml respectively).
- SUMM [0007] Initially, a sequence for a putative *Plasmodium falciparum* Fab I was located on the aggregate *P. falciparum* chromosomes referred to as "blob" (GenBank Accession Number AF338731). The deduced amino acid sequence and a multisequence alignment with representative. . . obtained with a BLAST search using the sequences from both the *B. napus* and *E. coli* enzymes within the *P. falciparum* database "PlasmoDB" (found at www.PlasmoDB.org). (See Materials and Methods). This sequence was then converted to an amino acid sequence at. . .
- SUMM . . . Interestingly, there is much greater sequence similarity with the plant enzyme than with the ENRs of bacterial origin. The *P. falciparum* enoyl acyl carrier protein reductase appears to have a plastid targeting sequence (Waller et al., 2000) and has a number of internal insertions. In addition, the *P. falciparum* protein has an extremely polar additional internal insertion for which no counterpart exists in any of the previously described enoyl. . .
- SUMM [0010] Because Fab I was located, the effects of triclosan on *Plasmodium falciparum* in vitro were investigated. For *P. falciparum*, the in vitro assays (Milhous et al., 1985; Oduola et al., 1988) were conducted using a modification of the semiautomated. . . N₂ for 48 h. [³H]-Hypoxanthine incorporation was measured as described previously (Milhous et al., 1985; Oduola et al., 1988). *P. falciparum* strain W2 is susceptible to mefloquine, but resistant to pyrimethamine, sulphadoxine and quinine and less susceptible to chloroquine than *P. falciparum* strain D6. Strain D6 is susceptible to pyrimethamine and sulphadoxine, but similar to *P. falciparum* strains TM90C2A and TM90C2B, and strain TM91C235 is less susceptible to mefloquine.
- SUMM [0011] The effect of triclosan on *P. falciparum* in vitro was studied with pyrimethamine sensitive and resistant organisms, and those with varying sensitivity to chloroquine and mefloquine, simultaneously with studies of effect of chloroquin or mefloquine on these parasites (Table 1). Triclosan was effective against pyrimethamine resistant *P. falciparum* (W2) at low concentrations (IC₅₀s of 150 nanograms/ml [triclosan] and 160 ngm/ml [Chloroquin], respectively) (Table 1). Interestingly, the pattern of relative susceptibility of triclosan and mefloquine were identical. This similarity suggests that triclosan and mefloquine may share a common mechanism of influx or efflux, because such differences in transporters are believed to be the basis of the differences in susceptibility of malaria parasites to mefloquin although other mechanisms are possible.
- SUMM [0014] Triclosan also was effective against *T. gondii*, in nanomolar amounts (FIG. 2). IC₅₀ was 62 nanograms/ml. There was no toxicity to. . .
- SUMM [0015] Analysis of the binding site for triclosan in *B. napus* and *E. coli* ENR shows that 11 residues have contacts less than 4 Å with one of more atoms of the triclosan (FIG. 3). Inspection of the sequence for *P. falciparum* ENR reveals that it shares sequence identity at each of these positions with either the sequence of the *B. napus* or *E. coli* enzymes providing a clear explanation for the inhibitory properties of this agent against *P. falciparum*.
- SUMM [0016] The discovery and characterization of an apicomplexan Fab I and discovery of triclosan as a lead compound provide means to

rationally design novel inhibitory compounds with considerable promise. The invention provides novel ways to counteract the increasing resistance of Plasmodium to the current armoury of antimalarial agents and provides a new approach to the great need for additional, less toxic antimicrobial agents effective against *T. gondii*. . . other novel inhibitors of sequential enzymatic steps in the apicomplexan lipid synthesis pathway, that are predicted to be synergistic with triclosan and other inhibitors of Fab I (Baldock, et al., 1996). This also raises the exciting possibility of a rational basis. . .

DRWD . . . shows a multiple structure-based sequence alignment of the enoyl reductases from *E. coli*, *H. pylori*, *B. subtilis*, *S. aureus*, *P. falciparum* and *B. napus*. The secondary structures and sequence numbers of the *E. coli* and *B. napus* enzymes are shown above. . . the alignment, respectively. The residues which are completely conserved are all black with white faced type and those involved in triclosan binding are indicated with a black, filled circle above. The N terminal sequence in the *P. falciparum* Fab I with no corresponding sequence in *E. coli* is a plastid target sequence which is a suitable separate target. . .

DRWD [0018] FIG. 2 demonstrates inhibition of *T. gondii* by triclosan. (a) no inhibitory effect of triclosan on the host cells uptake of thymidine; appearance of the monolayer also was unchanged. (b) effect of triclosan on *T. gondii* uracil uptake; triclosan reduces uracil uptake by intracellular *T. gondii* 4 days after infection; IC₅₀ was .congruent.62 nanograms per ml; effect increased between days 1 to 4, for example, in a separate experiment, for 125 nanograms per ml of triclosan on day 1, percentage inhibition was 20% and on day 4 was 72% and for pyrimethamine/sulfadiazine percentages of inhibition at. . .

DRWD . . . FIG. 3 is a stereo view of the three dimensional arrangement of the atoms that form the binding pocket for triclosan, in *E. coli* enoyl reductase, with the 11 residues that have any atom within 4 Å of the inhibitor, labeled. This is important in assigning the relative contributions made to the interaction with triclosan by the critical amino acids that are also present in the *P. falciparum* enzyme.

DRWD . . . activity by 1 mM glyosate. Squares, without glyphosate. Circles, with glyphosate; (E) shows evidence for the shikimate pathway in *P. falciparum* with functional evidence for the shikimate pathway in *P. falciparum*. Glyphosate inhibition of in vitro growth of asexual erythrocytic forms and PABA and folate antagonism of growth inhibition. Effect of. . .

DRWD [0025] FIG. 9 is an illustrative copy of a web page for the Plasmodium falciparum genomic sequence.

DRWD [0029] FIG. 13 shows a model of triclosan binding to its target enzyme, ENR.

DRWD [0031] FIG. 15 is the molecular formula and model for triclosan.

DETD [0032] A plant-like FAB I was identified in Plasmodium falciparum. The nucleotide sequence and deduced amino acid sequence was prepared and correct sequences were confirmed. FAB I is a single chain, discrete enzyme. All requisite residues for FAB I enzyme activity were confirmed. The *P. falciparum* enoyl acyl carrier protein reductase has a putative plastid targeting sequence and unique polar insertions. The FAB I structure is modeled on *E. coli* and *B. napus* FAB I structure alone and complexed to triclosan. Key amino acids were identified for 2° structure. Residues for binding triclosan were conserved providing explanation for inhibition by triclosan. Triclosan inhibits *P. falciparum*, *T. gondii* (nm) in a pattern similar to the action of mefloquine.

. Soluble protein can be overexpressed.

DETD [0033] Information obtained from *P. falciparum* because FAB I was purified include that the N terminal sequence is the same as B. napus FAB I, enzyme activity is NADH dependent and inhibited by triclosan. FAB I is involved in synthesis of 10, 12 C fatty acids. In a *P. berghei* murine model, Triclosan administered subcutaneously (3 or 38 mg/kg) was nontoxic, cleared parasitemia and prevented death. Synergy was demonstrated in vitro with cerulein, . . .

DETD [0036] *P. falciparum*. The in vitro assays (Oduala et al., 1988; Milhous et al., 1985) were conducted using a modification of the semiautomated. . . 5% CO₂ and 90% N₂ for 48h, [3H]-Hypoxanthine incorporation was measured as described previously (13, 14). W2 is susceptible to mefloquine, but resistant to pyrimethamine, sulphadoxine, but similar to TM90C2A and TM90C2B, and TM91C235 is less susceptible to mefloquin.

DETD [0037] TABLE 1: IC 50.sup.1 OF Triclosan, Chloroquine, AND Mefloquine When Cultured with *P. falciparum* (Nanograms/Ml)

DETD [0038] The activity of triclosan, mefloquine, and chloroquine were tested against a series of *P. falciparum* isolates and clones with differing susceptibilities to antimalarial drugs. D6, a clone from the African Sierra I/UNC isolate, is chloroquine and pyrimethamine susceptible; W2 is a clone of the Indochina I isolate and is chloroquine and pyrimethamine resistant. TM90C2A, TM90C2B, and TM91C235 are isolates from Thailand and all are chloroquine and mefloquine resistant. TM91C235 was isolated from a patient that failed mefloquine twice, whereas TM90-C2a and TM90-Cb are admission and recrudescence isolates, respectively, of the first patient who failed treatment with atovaquone. . . atovaquone, when compared with the admission isolate and other atovaquone--susceptible isolates from Thailand.

Antimicrobial Agents	Parasite Strain D6	TM90C2A	W2	TM90C2B	TM91C235
<u>Triclosan</u>	387.1	1891.4	154.4	1330.4	1800.5
<u>Mefloquine</u>	5.3	24.5	2.0	19.3	19.6
<u>Chloroquine</u>	3.8	57.3	162.4	82.7	46.1

DETD [0039] Cloning of the FabI gene. The FabI gene from *Plasmodium falciparum* is located on chromosome 4 and codes for a 432 amino acid protein. The FabI gene from gDNA of the 3D7 strain of *P. falciparum* was amplified using Pfu Turbo polymerase (Stratagene) and two primers (5'-GGTGGTGAATTCATGAATAAAATATCACAACGG-3' and 5'-GGTGGTGTGCGACTTATTCATTTTCATTGCGATATATATC-3'). The resulting amplicon was digested with EcoRI. . .

DETD [0043] Overexpression of Recombinant Fab I. The FabI gene was amplified from cDNA of the 3D7 strain of *P. falciparum* and inserted into the pMAL-c2x vector (New England Biolabs) for expression in *E. coli*. Recombinant FabI fused the Maltose Binding. . .

DETD . . . M., Zeidler J., Lichtenhaler H. K., Soldati D., Beck E., 1999. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science*. 285 (5433):1573-6.

DETD [0048] Jones R. D., Janpani H., Newman J. L., Lee A., 2000. Triclosan: A review of effectiveness and safety in healthcare settings. *Am J. Inf. Control*. 28, 184-196.

DETD . . . E., Baker P. J., Stuitje, A. R., Slabas, A. R., Rice, D. W., Rafferty, J. B., 1999. Molecular basis of triclosan activity.

Nature. 398, 383-384.

DETD [0051] McMurray L. M., Oethinger M., Levy S. B., 1998. Triclosan targets lipid synthesis. Nature. 394, 531-2.

DETD . . . Weatherly N. F., Bowdre J. H., Desjardins R. E., 1985. In vitro activities and mechanisms of resistance to anti-folates and anti-malarial drugs. Antimicrob. Agents Chemother. 27, 525-530.

DETD [0053] Oduola A. M. J., Weatherly N. J., Bowdre J. H., Desjardins R. E., 1988. Plasmodium falciparum--cloning by single erythrocyte micromanipulation and heterogeneity in vitro. Exp. Parasitol. 66, 86-95.

DETD [0055] Plasmodium Genome Database Collaborative, 2001. PlasmoDB: An integrative database of the P. falciparum genome. Tools for accessing and analyzing finished and unfinished sequence data. Nucl. Acids Res. 29: 66-69.

DETD . . . G. S., Roos D. S., McFadden G. I., 1998. Nuclear-encoded proteins target to the plastid in Toxoplasma gondii and Plasmodium falciparum. Proc Natl Acad Sci USA. 95(21), 12352-12357.

DETD . . . Waller R. F., Reed M. D., Cowman A. F., McFadden G. I., 2000. Protein trafficking to the plastid of Plasmodium falciparum is via the secretory pathway. EMBO J. 19(8): 1794-802.

DETD . . . J., Taylor, I. W. F., 1999. Kinetic and structural characteristics of the inhibition of enoyl (acyl carrier protein) reductase by triclosan. Biochemistry. 38, 12514-12525.

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 5

LENGTH: 420

TYPE: PRT

ORGANISM: Plasmodium falciparum

SEQUENCE: 5

Met Asn Lys Ile Ser Gln Arg Leu Leu Phe Leu Phe Leu His Phe Tyr

1 5

CLM What is claimed is:

. . . 1. A molecule of the Fab I enzyme having the amino acid sequence of the Fab I enzyme in Plasmodium falciparum, as shown in FIG. 1.

CLM What is claimed is:

3. The use of claim 2, wherein the apicomplexan is Plasmodium falciparum.

CLM What is claimed is:

5. A novel recombinant protein with an amino acid sequence substantially similar to that of Plasmodium falciparum shown FIG. 1.

CLM What is claimed is:

8. Use of the plasmid targeting sequence of the Plasmodium falciparum Fab I amino acid sequence according to FIG. 1, to design antimicrobial agents and inhibitors of apicomplexan growth and survival.

.

CLM What is claimed is:

9. Use of triclosan to inhibit apicomplexan growth and survival.

IT 3380-34-5, Triclosan

(as specific inhibitor of Fab I, use to inhibit apicomplexan growth and survival; cloning and sequencing of Plasmodium falciparum Fab I (enoyl acyl carrier protein reductase) gene and method for inhibition of apicomplexan parasites)

L15 ANSWER 7 OF 11 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 3

ACCESSION NUMBER: 2004:409132 BIOSIS
 DOCUMENT NUMBER: PREV200400410242
 TITLE: The efficacy of inhibitors involved in spermidine metabolism in *Plasmodium falciparum*, *Anopheles stephensi* and *Trypanosoma evansi*.
 AUTHOR(S): Moritz, E.; Seidensticker, S.; Gottwald, A.; Maier, W.; Hoerauf, A.; Njuguna, J. T.; Kaiser, A. [Reprint Author]
 CORPORATE SOURCE: Inst Med Parasitol, Sigmund Freud Str 25, D-53105, Bonn, Germany
 akaaiser@parasit.meb.uni-bonn.de
 SOURCE: Parasitology Research, (September 2004) Vol. 94, No. 1, pp. 37-48. print.
 ISSN: 0932-0113 (ISSN print).
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 20 Oct 2004
 Last Updated on STN: 20 Oct 2004

TI The efficacy of inhibitors involved in spermidine metabolism in *Plasmodium falciparum*, *Anopheles stephensi* and *Trypanosoma evansi*.
 AB. . . have tested the effect of different polyamine inhibitors of the spermidine metabolizing enzymes deoxyhypusine synthase and homospermidine synthase in different chloroquine resistant *Plasmodium falciparum* strains, in the mosquito *Anopheles stephensi* (Diptera: Culicidae) and in a *Trypanosoma evansi* clone I from strain STIB 806 K China. Recent experiments have shown that agmatine is a growth inhibitor of the malaria parasite *P. falciparum* (Kaiser et al. 2001) in vitro. A comparison of agmatine efficacy with the new antimalarials artemisinin, triclosan and conventional chloroquine showed similar or even better results on the basis of growth inhibition and the reduction of developmental forms. However, no effect of triclosan or agmatine was observed at the ribonucleic acid level. In a second set of experiments, we tested the effect of. . .

IT . . .
 and Lymphatics (Transport and Circulation); Infection; Parasitology; Pharmacology
 IT Diseases
 African sleeping sickness: parasitic disease, diagnosis, drug therapy
 IT Diseases
malaria: blood and lymphatic disease, parasitic disease, diagnosis, drug therapy
Malaria (MeSH)
 IT Chemicals & Biochemicals
 1,3-diaminopropane: antiinfective-drug, antiparasitic-drug;
 1,7-diaminoheptane: antiinfective-drug, antiparasitic-drug,
antimalarial, deoxyhypusine inhibitor; 1,8-diaminooctane:
 antiinfective-drug, antiparasitic-drug; agmatine: antiinfective-drug,
 antiparasitic-drug, antimalarial, antiparasitic effect,
 efficacy, growth inhibitor; artemisinin: antiinfective-drug,
antimalarial; chloroquine: antiinfective-drug,
 antiparasitic-drug, antimalarial; deoxyhypusine synthase [EC
 2.5.1.46]; dicyclohexylamine: antiinfective-drug, antiparasitic-drug,
antimalarial, spermidine biosynthesis inhibitor; homospermidine
 synthase [EC 2.5.1.44]; polyamine inhibitor; ribonucleic acid;
 spermidine: biosynthesis inhibition, metabolism inhibition;
triclosan: antiinfective-drug, antiparasitic-drug,
antimalarial
 ORGN . . .
 Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

09763499

ORGN Classifier

Sporozoa 35400

Super Taxa

Protozoa; Invertebrata; Animalia

Organism Name

Plasmodium falciparum (species): pathogen, oocyst,
strain-Dd2, strain-NF54, strain-R

Taxa Notes

Animals, Invertebrates, Microorganisms, Protozoans

RN 109-76-2 (1,3-diaminopropane)
646-19-5 (1,7-diaminoheptane)
373-44-4 (1,8-diaminooctane)
306-60-5 (agmatine)
63968-64-9 (artemisinin)
54-05-7 (chloroquine)
127069-31-2 (deoxyhypusine synthase)
127069-31-2 (EC 2.5.1.46)
101-83-7 (dicyclohexylamine)
76106-84-8 (homospermidine synthase)
76106-84-8 (EC 2.5.1.44)
124-20-9 (spermidine)
3380-34-5 (triclosan)

L15 ANSWER 8 OF 11 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights
reserved on STN

ACCESSION NUMBER: 2003272093 EMBASE

TITLE: Targeting tuberculosis and malaria through
inhibition of enoyl reductase. Compound activity and
structural data.

AUTHOR: Kuo, Mack R.; Iwamoto, Hiroyuki; Perozzo, Remo;
Sacchettini, James C. (correspondence)

CORPORATE SOURCE: Dept. of Biochem. and Biophysics, Texas A and M University,
College Station, TX 77843, United States. sacchett@tamu.edu

AUTHOR: Morbidoni, Hector R.; Jacobs Jr., William R.; Fidock, David
A.

CORPORATE SOURCE: Dept. of Microbiol. and Immunology, Bronx, NY 10461, United
States.

AUTHOR: Jacobs Jr., William R.

CORPORATE SOURCE: Howard Hughes Medical Institute, Albert Einstein College of
Medicine, Bronx, NY 10461, United States.

AUTHOR: Alland, David

CORPORATE SOURCE: Division of Infectious Diseases, Center for Emerging
Pathogens, New Jersey Medical School, Newark, NJ 07103,
United States.

AUTHOR: Sneddon, Scott F.; Goullie, Brian B.; Staveski, Mark M.;
Leonard, Marina; Gregory, Jill S.; Janjigian, Andrew D.;
Yee, Christopher

CORPORATE SOURCE: Genzyme Drug Discovery, Genzyme Corp., Cambridge, MA
02139-1562, United States.

AUTHOR: Musser, James M.

CORPORATE SOURCE: Lab. of Human Bact. Pathogenesis, Division of Intramural
Research, National Institutes of Health, Hamilton, MT
59840, United States.

AUTHOR: Kreiswirth, Barry

CORPORATE SOURCE: Pub. Hlth. Res. Institute TB Center, New York, NY 10016,
United States.

AUTHOR: Sacchettini, James C. (correspondence)

CORPORATE SOURCE: Dept. of Biochem. and Biophysics, Texas A and M University,
Biochemistry and Biophysics Bldg., College Station, TX
77843, United States. sacchett@tamu.edu

SOURCE: Journal of Biological Chemistry, (6 Jun 2003) Vol. 278, No. 23, pp. 20851-20859.
 Refs: 46
 ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Clinical and Experimental Pharmacology
 037 Drug Literature Index
 004 Microbiology: Bacteriology, Mycology, Parasitology and Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 24 Jul 2003
 Last Updated on STN: 24 Jul 2003

- TI Targeting tuberculosis and malaria through inhibition of enoyl reductase. Compound activity and structural data.
- AB Tuberculosis and malaria together result in an estimated 5 million deaths annually. The spread of multidrug resistance in the most pathogenic causative agents, *Mycobacterium tuberculosis* and *Plasmodium falciparum*, underscores the need to identify active compounds with novel inhibitory properties. Although genetically unrelated, both organisms use a type II. . . with a combinatorial library, we have identified two novel classes of compounds with activity against the *M. tuberculosis* and *P. falciparum* enzyme (referred to as InhA and PfENR, respectively). The crystal structure of InhA complexed with NAD(+) and one of the inhibitors was determined to elucidate the mode of binding. Structural analysis of InhA with the broad spectrum antimicrobial triclosan revealed a unique stoichiometry where the enzyme contained either a single triclosan molecule, in a configuration typical of other bacterial ENR:triclosan structures, or harbored two triclosan molecules bound to the active site. Significantly, these compounds do not require activation and are effective against wild-type and drug-resistant strains of *M. tuberculosis* and *P. falciparum*. Moreover, they provide broader chemical diversity and elucidate key elements of inhibitor binding to InhA for subsequent chemical optimization.
- CT Medical Descriptors:
- article
 - bacterial growth
 - crystal structure
 - drug structure
 - enzyme active site
 - *enzyme inhibition
 - *malaria
 - minimum inhibitory concentration
 - Mycobacterium tuberculosis*
 - nonhuman
 - Plasmodium falciparum*
 - priority journal
 - stoichiometry
 - structure analysis
 - *tuberculosis
 - antiinfective agent: AN, drug analysis
 - carrier protein: EC, endogenous compound
 - chloroquine: CM, drug comparison
 - cycloguanil: CM, drug comparison
 - *enoyl acyl carrier protein reductase: CM, drug comparison
 - *enoyl acyl carrier protein reductase: DV, drug development
 - *enoyl. . . 8575: DV, drug development
 - *genz 8575: PD, pharmacology

isoniazid
 *protein inhA: CM, drug comparison
 *protein inhA: DV, drug development
 *protein inhA: PD, pharmacology
 pyrimethamine: CM, drug comparison
quinine: CM, drug comparison
 sulfadoxine: CM, drug comparison
triclosan: AN, drug analysis
 unclassified drug

RN (carrier protein) 80700-39-6; (chloroquine) 132-73-0, 3545-67-3,
 50-63-5, 54-05-7; (cycloguanil) 516-21-2; (fatty acid synthase) 9045-77-6;
 (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (pyrimethamine) 53640-38-3,
 58-14-0; (quinine) 130-89-2, 130-95-0, 14358-44-2, 549-48-4,
 549-49-5, 60-93-5, 7549-43-1; (sulfadoxine) 2447-57-6; (triclosan
) 3380-34-5

L15 ANSWER 9 OF 11 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002309077 EMBASE

TITLE: Structural elucidation of the specificity of the antibacterial agent triclosan for malarial enoyl acyl carrier protein reductase.

AUTHOR: Perozzo, Remo; Kuo, Mack; Sidhu, Amar bir Singh; Valiyaveettil, Jacob T.; Bittman, Robert; Jacobs Jr., William R.; Fidock, David A.; Sacchettini, James C. (correspondence)

CORPORATE SOURCE: Department of Biochemistry, Texas A and M University, College Station, TX 77843-2128, United States. sacchett@tam u.edu

SOURCE: Journal of Biological Chemistry, (12 Apr 2002) Vol. 277, No. 15, pp. 13106-13114.
 Refs: 62

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

004 Microbiology: Bacteriology, Mycology, Parasitology and Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 19 Sep 2002

Last Updated on STN: 19 Sep 2002

TI Structural elucidation of the specificity of the antibacterial agent triclosan for malarial enoyl acyl carrier protein reductase.

AB The human malaria parasite Plasmodium falciparum synthesizes fatty acids using a type II pathway that is absent in humans. The final step in fatty acid elongation. . . enoyl acyl carrier protein reductase, a validated antimicrobial drug target. Here, we report the cloning and expression of the P. falciparum enoyl acyl carrier protein reductase gene, which encodes a 50-kDa protein (PfENR) predicted to target to the unique parasite apicoplast. Purified PfENR was crystallized, and its structure resolved as a binary complex with NADH, a ternary complex with triclosan and NAD(+), and as ternary complexes bound to the triclosan analogs 1 and 2 with NADH. Novel structural features were identified in the PfENR binding loop region that most closely. . . homologs; elsewhere the protein was similar to ENR from the plant Brassica napus (root mean square for Cas, 0.30 A). Triclosan and its analogs 1 and 2 killed multidrug-resistant strains of intra-erythrocytic P. falciparum

parasites at sub to low micromolar concentrations in vitro. These data define the structural basis of triclosan binding to PfENR and will facilitate structure-based optimization of PfENR inhibitors.

CT Medical Descriptors:

antiprotozoal activity
 apicoplast
 article
 binding site
 Brassica
 catalysis
 crystallization
 drug specificity
 drug structure
 drug targeting
 fatty acid synthesis
 gene expression
 *malaria
 molecular cloning
 multidrug resistance
 nonhuman
 *Plasmodium falciparum
 priority journal
 protein binding
 sequence homology
 4 chloro 2 hydroxyphenyl 6' hydroxynaphthyl ether: AN, drug analysis
 4 chloro 2 hydroxyphenyl 6' hydroxynaphthyl ether: DV, drug development
 *acyl carrier protein
 *antiinfective agent: AN, drug analysis
 chloroquine
 cycloguanil
 drug derivative: AN, drug analysis
 drug derivative: DV, drug development
 fatty acid
 n (2,4 dichlorophenyl) 2' hydroxyaniline: AN, drug analysis
 n (2,4 dichlorophenyl) 2' hydroxyaniline: DV, drug development
 nicotinamide adenine dinucleotide
 *oxidoreductase
 oxidoreductase inhibitor: AN, drug analysis
 oxidoreductase inhibitor: DV, drug development
 pyrimethamine
 quinine
 reduced nicotinamide adenine dinucleotide
 sulfadoxine
 *triclosan: AN, drug analysis
 unclassified drug

RN (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7;
 (cycloguanil) 516-21-2; (nicotinamide adenine dinucleotide) 53-84-9;
 (oxidoreductase) 9035-73-8, 9035-82-9, 9037-80-3, 9055-15-6;
 (pyrimethamine) 53640-38-3, 58-14-0; (quinine) 130-89-2,
 130-95-0, 14358-44-2, 549-48-4, 549-49-5, 60-93-5, 7549-43-1; (reduced
 nicotinamide adenine dinucleotide) 58-68-4; (sulfadoxine) 2447-57-6; (
triclosan) 3380-34-5

L15 ANSWER 10 OF 11 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001064519 EMBASE

TITLE: Triclosan offers protection against blood stages of malaria by inhibiting enoyl-ACP reductase of Plasmodium falciparum.

AUTHOR: Surolia, N. (correspondence); Surolia, A.

CORPORATE SOURCE: Molecular Biology and Genetics Unit, Jawaharlal Nehru Ctr.
Adv. Sci. Res., Jakkur, Bangalore, India. surolia@jncasr.ac
.in

SOURCE: Nature Medicine, (2001) Vol. 7, No. 2, pp. 167-173.
Refs: 40
ISSN: 1078-8956 CODEN: NAMEFI

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index
004 Microbiology: Bacteriology, Mycology, Parasitology
and Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Mar 2001
Last Updated on STN: 1 Mar 2001

TI Triclosan offers protection against blood stages of
malaria by inhibiting enoyl-ACP reductase of Plasmodium
falciparum.

AB The antimicrobial biocide triclosan [5-chloro-2-(2,4-
dichlorophenoxy)phenol] potently inhibits the growth of Plasmodium
falciparum in vitro and, in a mouse model, Plasmodium
berghei in vivo. Inhibition of [(14)C]acetate and
[(14)C]malonyl-CoA incorporation into fatty acids in vivo and in vitro,
respectively, by triclosan implicate FabI as its target. Here
we demonstrate that the enoyl-ACP reductase purified from P.
falciparum is triclosan sensitive. Also, we present the
evidence for the existence of FabI gene in P. falciparum. We
establish the existence of the de novo fatty acid biosynthetic pathway in
this parasite, and identify a key enzyme of this pathway for the
development of new antimalarials.

CT Medical Descriptors:
amino acid sequence
animal cell
animal model
animal tissue
article
controlled study
drug mechanism
drug potency
drug protein binding
enzyme inhibition
fatty acid synthesis
growth inhibition
life cycle
*malaria: PC, prevention
mouse
nonhuman
Plasmodium berghei
*Plasmodium falciparum
priority journal
acetic acid
*acyl carrier protein: EC, endogenous compound
*antimalarial agent: CM, drug comparison
*antimalarial agent: DV, drug development
*antimalarial agent: PD, pharmacology
carbon 14
cerulenin: CM, drug comparison
cerulenin: PD, pharmacology
chloroquine: CM, drug comparison
chloroquine: PD, pharmacology

*enoyl acyl carrier protein reductase: EC, endogenous compound
 malonyl coenzyme A
 nicotinamide adenine dinucleotide: EC, endogenous compound
 reduced nicotinamide adenine dinucleotide: EC, endogenous compound
 reduced nicotinamide adenine dinucleotide phosphate: EC, endogenous compound

*triclosan: CM, drug comparison
*triclosan: DV, drug development
*triclosan: PD, pharmacology

unclassified drug

RN (acetic acid) 127-08-2, 127-09-3, 64-19-7, 71-50-1; (carbon 14) 14762-75-5; (cerulenin) 17397-89-6; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (malonyl coenzyme A) 524-14-1; (nicotinamide adenine dinucleotide) 53-84-9; (reduced nicotinamide adenine dinucleotide phosphate) 53-57-6; (reduced nicotinamide adenine dinucleotide) 58-68-4; (triclosan) 3380-34-5

L15 ANSWER 11 OF 11 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001064504 EMBASE
 TITLE: New agents to combat malaria.
 AUTHOR: Beeson, J.G. (correspondence); Winstanley, P.A.; McFadden, G.I.; Brown, G.V.
 CORPORATE SOURCE: Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Victoria, Australia. beeson@unimelb.edu.au
 SOURCE: Nature Medicine, (2001) Vol. 7, No. 2, pp. 149-150.
 Refs: 9
 ISSN: 1078-8956 CODEN: NAMEFI
 COUNTRY: United States
 DOCUMENT TYPE: Journal; (Short Survey)
 FILE SEGMENT: 030 Clinical and Experimental Pharmacology
 036 Health Policy, Economics and Management
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 1 Mar 2001
 Last Updated on STN: 1 Mar 2001

TI New agents to combat malaria.

AB Triclosan, an antibacterial agent found in mouthwashes, acne medicines and deodorants, also prevents the growth of Plasmodium falciparum. If properly developed, this type II fatty acid biosynthesis inhibitor may be a promising new antimalarial agent.

CT Medical Descriptors:
 antibacterial activity
 drug cost
 drug efficacy
 drug mechanism
 human
 human cell
 human tissue

*malaria: DM, disease management
*malaria: DR, drug resistance
*malaria: DT, drug therapy
Plasmodium falciparum

priority journal
 short survey

*antimalarial agent: CM, drug comparison
*antimalarial agent: DV, drug development

*antimalarial agent: DT, drug therapy
*antimalarial agent: PE, pharmacoeconomics
*antimalarial agent: PD, pharmacology
artemether: DT, drug therapy
artemether: PD, pharmacology
 atovaquone: DT, drug therapy
 atovaquone: PD, pharmacology
 benflumetol: DT, drug therapy
 benflumetol: PD, pharmacology
chloroquine: DT, drug therapy
chloroquine: PD, pharmacology
 fansidar: DT, drug therapy
 fansidar: PD, pharmacology
 *fatty acid synthesis inhibitor
 halofantrine: DT, drug therapy
 halofantrine: PD, pharmacology
mefloquine: DT, drug therapy
mefloquine: PD, pharmacology
 proguanil: DT, drug therapy
 proguanil: PD, pharmacology
quinine: DT, drug therapy
quinine: PD, pharmacology
 *thiolactomycin: PD, pharmacology
*triclosan: CM, drug comparison
*triclosan: DV, drug development
*triclosan: DT, drug therapy
*triclosan: PE, pharmacoeconomics
*triclosan: PD, pharmacology
 unclassified drug
 RN (artemether) 71963-77-4; (atovaquone) 94015-53-9, 95233-18-4;
 (benflumetol) 82186-77-4; (chloroquine) 132-73-0, 3545-67-3,
 50-63-5, 54-05-7; (fansidar) 37338-39-9; (halofantrine) 36167-63-2,
 66051-63-6, 66051-74-9, 66051-76-1, 69756-53-2; (mefloquine)
 51773-92-3, 53230-10-7; (proguanil) 500-92-5, 637-32-1; (quinine
) 130-89-2, 130-95-0, 14358-44-2, 549-48-4, 549-49-5, 60-93-5, 7549-43-1;
 (thiolactomycin) 82079-32-1; (triclosan) 3380-34-5

=> d his

(FILE 'HOME' ENTERED AT 12:12:49 ON 20 SEP 2008)

FILE 'REGISTRY' ENTERED AT 12:13:14 ON 20 SEP 2008

L1 5 S TRICLOSAN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CAPLUS, DDFB, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIODASE, IFIPAT, IMSDRUGNEWS, IMSPRODUCT, IPA, KOSMET, LIFESCI, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, PHARMAML, ...' ENTERED AT 12:14:55 ON 20 SEP 2008

L2 13207 S L1
 L3 19219 S TRICLOSAN
 L4 21003 S L2 OR L3
 L5 357840 S MALARIA?
 L6 124642 S ANTIMALARIA?
 L7 408372 S L5 OR L6
 L8 474 S L4 AND L7
 L9 207454 S FALCIPARUM OR BERGHEI
 L10 312 S L8 AND L9
 L11 6149 S TRICLOSAN/AB

09763499

L12 166 S L10 AND L11
L13 217939 S QUININE OR ATABRINE OR CHLOROQUINE OR MEFLOQUINE OR PRIMAQUIN
L14 22 S L12 AND L13
L15 11 DUP REM L14 (11 DUPLICATES REMOVED)

=> s l12 and pd<19990623

6 FILES SEARCHED...
'19990623' NOT A VALID FIELD CODE
'19990623' NOT A VALID FIELD CODE
'19990623' NOT A VALID FIELD CODE
16 FILES SEARCHED...
'19990623' NOT A VALID FIELD CODE
22 FILES SEARCHED...
'19990623' NOT A VALID FIELD CODE
'19990623' NOT A VALID FIELD CODE
'19990623' NOT A VALID FIELD CODE
31 FILES SEARCHED...
35 FILES SEARCHED...
L16 0 L12 AND PD<19990623

=> s l8 and PD<1999

'1999' NOT A VALID FIELD CODE
8 FILES SEARCHED...
'1999' NOT A VALID FIELD CODE
'1999' NOT A VALID FIELD CODE
'1999' NOT A VALID FIELD CODE
21 FILES SEARCHED...
22 FILES SEARCHED...
'1999' NOT A VALID FIELD CODE
'1999' NOT A VALID FIELD CODE
'1999' NOT A VALID FIELD CODE
31 FILES SEARCHED...
L17 15 L8 AND PD<1999

=> dup rem

ENTER L# LIST OR (END):l17

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2, IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

PROCESSING COMPLETED FOR L17

L18 14 DUP REM L17 (1 DUPLICATE REMOVED)

=> d l18 1-14 ibib, kwic

L18 ANSWER 1 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:82359 USPATFULL

TITLE: Enhanced skin penetration system for improved topical delivery of drugs

INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States

PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5780049		19980714 <--
APPLICATION INFO.:	US 1995-464991		19950605 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned		

Jagoe

which is a continuation of Ser. No. US 1993-111032,
 filed on 24 Aug 1993, now abandoned which is a
 continuation of Ser. No. US 1992-957752, filed on 2 Oct
 1992, now abandoned which is a continuation of Ser. No.
 US 1991-778424, filed on 16 Oct 1991, now abandoned

DOCUMENT TYPE: Utility
 FILE SEGMENT: Granted
 PRIMARY EXAMINER: Rose, Shep K.
 LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbieri, David K.
 NUMBER OF CLAIMS: 13
 EXEMPLARY CLAIM: 1
 LINE COUNT: 698
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans);
 antibiotics and antimicrobials such as benzoyl peroxide, octopirox,
 erythromycin, tetracyclin, triclosan, azelaic acid and its
 derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate,
 clindamycin and meclocycline; sebastats such as flavinoids; hydroxy
 acids; . . .

SUMM . . . inclusion in compositions of the present invention include
 pharmaceutically-acceptable salts of β -lactam drugs, quinolone
 drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin,
triclosan, doxycycline, capreomycin, chlorhexidine,
 chlortetracycline, oxytetracycline, clindamycin, ethambutol,
 metronidazole, pentamidine, gentamicin, kanamycin, lineomycin,
 methacycline, methenamine, minocycline, neomycin, netilmicin,
 paromomycin, streptomycin, tobramycin,. . . methenamine mandelate,
 minocycline hydrochloride, neomycin sulfate, netilmicin sulfate,
 paromomycin sulfate, streptomycin sulfate, tobramycin sulfate,
 miconazole hydrochloride, amanfadine hydrochloride, amanfadine sulfate,
triclosan, octopirox, parachlorometa xylenol, nystatin,
 tolnaftate and clotrimazole.

SUMM Useful drug actives in the compositions of the present invention include
antimalarial drugs. Antimalarial drugs preferred for
 inclusion in compositions of the present invention include
 pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine
 primaquine and quinine.

CLM What is claimed is:
 . . . of an antimicrobial pharmaceutical active selected from the group
 consisting of β -lactam drugs, quinolone drugs, ciprofloxacin,
 norfloxacin, tetracycline, erythromycin, amikacin, triclosan,
 doxycycline, capremycin, chlorhexidine, chlortetracycline,
 oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine,
 gentamicin, kanamycin, lineomycin, methacycline, methenamine,
 minocycline, neomycin, netilmicin, paromomycin, streptomycin,
 tobramycin, miconazole, amanfadine, triclosan, octopirox,
 parachlorometa xylenol, nystatin, tolnaftate, clotrimazole,
 pharmaceutically-acceptable salts thereof, and mixtures thereof; and (c)
 from about 0.05% to about 5%. . .

CLM What is claimed is:
 . . . said antimicrobial pharmaceutical active is selected from the group
 consisting of β -lactam drugs, quinolone drugs, ciprofloxacin,
 norfloxacin, tetracycline, erythromycin, amikacin, triclosan,
 doxycycline, capremycin, chlorhexidine, chlortetracycline,
 oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine,
 gentamicin, kanamycin, lineomycin, methacycline, methenamine,
 minocycline, neomycin, netilmicin, paromomycin, streptomycin,
 tobramycin,. . .

CLM What is claimed is:

. . . methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amantadine hydrochloride, amantadine sulfate, triclosan, octopirox, parachlorometa xyleneol, nystatin, tolmetate and clotrimazole.

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.1^{3,7}]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 2 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:78738 USPATFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
	-----	-----	-----
PATENT INFORMATION:	US 5776485		19980707 <--
APPLICATION INFO.:	US 1995-469701		19950606 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Rose, Shep K.		
LEGAL REPRESENTATIVE:	Henderson, Loretta J., Dabbieri, David K.		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
LINE COUNT:	700		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans); antibiotics and antimicrobials such as benzoyl peroxide, octopirox, erythromycin, tetracyclin, triclosan, azelaic acid and its derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate, clindamycin and meclocycline; sebastats such as flavinoids; hydroxy acids;. . .

SUMM . . . inclusion in compositions of the present invention include pharmaceutically-acceptable salts of β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin,

methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin,. . . methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amantadine hydrochloride, amantadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and clotrimazole.

SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.1^{3,7}]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 3 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:75176 USPATFULL

TITLE: Enhanced skin penetration system for improving topical delivery of drugs

INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States

PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5773023		19980630 <--
APPLICATION INFO.:	US 1995-462710		19950605 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Rose, Shep K.		
LEGAL REPRESENTATIVE:	Henderson, Loretta J., Dabbieri, David K.		
NUMBER OF CLAIMS:	29		
EXEMPLARY CLAIM:	1		
LINE COUNT:	745		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans); antibiotics and antimicrobials such as benzoyl peroxide, octopirox, erythromycin, tetracyclin, triclosan, azelaic acid and its derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate, clindamycin and meclocycline; sebastats such as flavinoids; hydroxy acids;. . .

SUMM . . . inclusion in compositions of the present invention include pharmaceutically-acceptable salts of β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin,. . . methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amantadine hydrochloride, amantadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and clotrimazole.

SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.

CLM What is claimed is:
. . . diuretic drugs, vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs, anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs, antipsychotic drugs, antineoplastic drugs, antimalarial drugs, muscle relaxant drugs, antispasmodic drugs, antidiarrheal drugs, bone-active drugs and mixtures thereof; and (c) from about 0.05% to about. . .

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.1.3,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 4 OF 14 USPTAFULL on STN

ACCESSION NUMBER: 1998:57546 USPTAFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5756119		19980526 <--
APPLICATION INFO.:	US 1995-462376		19950605 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		

PRIMARY EXAMINER: Rose, Shep K.
 LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbieri, David K.
 NUMBER OF CLAIMS: 14
 EXEMPLARY CLAIM: 1
 LINE COUNT: 697
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans); antibiotics and antimicrobials such as benzoyl peroxide, octopirox, erythromycin, tetracyclin, triclosan, azelaic acid and its derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate, clindamycin and meclocycline; sebastats such as flavinoids; hydroxy acids; . . .

SUMM . . . inclusion in compositions of the present invention include pharmaceutically-acceptable salts of β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, . . . methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amantadine hydrochloride, amantadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and clotrimazole.

SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.1^{3,7}]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
 (antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 5 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:57545 USPATFULL
 TITLE: Enhanced skin penetration system for improved topical delivery of drugs
 INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
 Lombardo, Brian Scott, Ansonia, CT, United States
 PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5756118		19980526 <--
APPLICATION INFO.:	US 1995-462258		19950605 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032,		

filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned

DOCUMENT TYPE: Utility
 FILE SEGMENT: Granted
 PRIMARY EXAMINER: Rose, Shep K.
 LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbieri, David K.
 NUMBER OF CLAIMS: 16
 EXEMPLARY CLAIM: 1
 LINE COUNT: 682
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans); antibiotics and antimicrobials such as benzoyl peroxide, octopirox, erythromycin, tetracyclin, triclosan, azelaic acid and its derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate, clindamycin and meclocycline; sebastats such as flavinoids; hydroxy acids; . . .

SUMM . . . inclusion in compositions of the present invention include pharmaceutically-acceptable salts of β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, . . . methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amanfadine hydrochloride, amanfadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and clotrimazole.

SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.1^{3,7}]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
 (antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 6 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:47986 USPATFULL
 TITLE: High viscosity liquid controlled delivery system
 INVENTOR(S): Tipton, Arthur J., Birmingham, AL, United States
 Holl, Richard J., Birmingham, AL, United States
 PATENT ASSIGNEE(S): Southern Biosystems, Inc., Birmingham, AL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5747058		19980505 <--

09763499

APPLICATION INFO.: US 1995-474337 19950607 (8)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Azpuru, Carlos A.
LEGAL REPRESENTATIVE: Kilpatrick Stockton LLP, Meredith, Esq., Roy D.
NUMBER OF CLAIMS: 95
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1344
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . and PGF.sub.2 ; antipyretics such as aspirin, sodium salicylate, and salicylamide; antispasmodics such as atropine, methantheline, papaverine, and methscopolamine bromide; antimalarials such as the 4-aminoquinolines, 8-aminoquinolines, chloroquine, and pyrimethamine, antihistamines such as diphenhydramine, dimenhydrinate, tripeleennamine, perphenazine, and chlorphenazine; cardioactive agents such. . .
DETD Antimicrobial active agents that are currently used in mouthwash formulations can include, but not limited to, domiphen bromide, triclosan, chlorhexidine, essential oils, cetyl pyridinium chloride, fluorides, alexidine, salicylanilides, zinc compounds, and antibiotics. They can be used either singly or. . .

L18 ANSWER 7 OF 14 USPATFULL on STN

ACCESSION NUMBER: 1998:17360 USPATFULL
TITLE: Compositions and methods for topical administration of pharmaceutically active agents
INVENTOR(S): Kanios, David P., Miami, FL, United States
Gentile, Joseph A., Plantation, FL, United States
Mantelle, Juan A., Miami, FL, United States
Sablotsky, Steven, Miami, FL, United States
PATENT ASSIGNEE(S): Noven Pharmaceuticals, Inc., Miami, FL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5719197		19980217 <--
APPLICATION INFO.:	US 1995-477361		19950607 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-112330, filed on 27 Aug 1993, now patented, Pat. No. US 5446070 which is a continuation-in-part of Ser. No. US 1991-813196, filed on 23 Dec 1991, now patented, Pat. No. US 5234957 which is a continuation-in-part of Ser. No. US 1991-661827, filed on 27 Feb 1991, now abandoned , said Ser. No. US 1995-477361, filed on 7 Jun 1995 which is a continuation-in-part of Ser. No. US 1993-67001, filed on 26 May 1993 which is a continuation of Ser. No. US 1991-671709, filed on 2 Apr 1991, now patented, Pat. No. US 5300291 which is a continuation-in-part of Ser. No. US 1989-295847, filed on 11 Jan 1989, now patented, Pat. No. US 4994267 which is a continuation-in-part of Ser. No. US 1988-164482, filed on 4 Mar 1988, now patented, Pat. No. US 4814168		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Azpuru, Carlos A.		
LEGAL REPRESENTATIVE:	Foley & Lardner		
NUMBER OF CLAIMS:	27		
EXEMPLARY CLAIM:	1		

Jagoe

09763499

LINE COUNT: 1799
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD ANTIMALARIAL such as Acedapsone, Alphaaminoquinolines,
4-Aminoquinolines, Amodiaquin, Arteether, Artemether, Artemisinin,
Artesunate, Bebeerine, Berberine, Chirata, Chlorguanide, Chloroquine,
Chlorproguanil, Cinchona, Cinchonidine, Cinchonine, Cycloguanil, . . .
DETD . . . as Bornyl Chloride, Calcium Iodate, Iodine, Iodine
Monochloride, Iodine Trichloride, Iodoform, Povidone-Iodine, Sodium
Hypochlorite, Sodium Iodate, Symclosene, Thymol Iodide, Triclocarban,
Triclosan, Troclosesene Potassium
CLM What is claimed is:
. . . cholinergic blocking drugs, mydriatics, psychic energizers, humoral
agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic
drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine
drugs, antimalarial, antiulcer drugs, peptides, and
anti-estrogens.

L18 ANSWER 8 OF 14 USPATFULL on STN
ACCESSION NUMBER: 1998:4239 USPATFULL
TITLE: Gel type cosmetic compositions
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S.
corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5707635		19980113 <--
APPLICATION INFO.:	US 1994-249093		19940525 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-121661, filed on 15 Sep 1993, now abandoned which is a continuation of Ser. No. US 1992-931553, filed on 18 Aug 1992, now abandoned which is a continuation of Ser. No. US 1991-778423, filed on 16 Oct 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Hulina, Amy		
LEGAL REPRESENTATIVE:	Henderson, Loretta J., Dabbieri, David K.		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
LINE COUNT:	513		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs,
anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs,
antipsychotic drugs, antimicrobial drugs, antineoplastic drugs,
antimalarial drugs, muscle relaxant drugs, antispasmodic drugs,
antidiarrheal drugs and bone-active drugs and mixtures thereof.
SUMM . . . as retinoic acid and its derivatives (e.g., cis and trans);
antibiotics and antimicrobials such as benzoyl peroxide, octopirox,
erythromycin, tetracyclin, triclosan, azelaic acid and its
derivatives, phenoxy ethanol and phenoxy propanol, ethylacetate,
clindamycin and meclocycline; sebastats such as flavinoids; alpha and.
. . .

L18 ANSWER 9 OF 14 IFIPAT COPYRIGHT 2008 IFI on STN DUPLICATE 1
AN 02825061 IFIPAT;IFIUDB;IFICDB
TITLE: COMPOSITIONS FOR TOPICAL DELIVERY OF DRUGS COMPRISING

Jagoe

INVENTOR(S): A MIXTURE OF HIGH AND LOW HLB SURFACTANTS AND
ALKOXYLATED ETHER; TRANSDERMAL
Bloom, Roberta C, Huntington, CT
Deckner, George E, Cincinnati, OH
PATENT ASSIGNEE(S): The Procter & Gamble Company, Cincinnati, OH
PRIMARY EXAMINER: Kulkosky, Peter F
AGENT: Dabbieri, David K
Sabatelli, Anthony D

	NUMBER	PK	DATE
PATENT INFORMATION:	US 5614178	A	19970325
	(CITED IN 027 LATER PATENTS)		
APPLICATION INFORMATION:	US 1994-265975		19940627
EXPIRATION DATE:	25 Mar 2014		

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 1992-950527	19920925	ABANDONED
CONTINUATION OF:	US 1993-79977	19930625	ABANDONED
CONTINUATION-IN-PART OF:	US 1992-920937	19920728	ABANDONED
CONTINUATION-IN-PART OF:	US 1993-33211	19930318	ABANDONED
FAMILY INFORMATION:	US 5614178	19970325	
DOCUMENT TYPE:	Utility Certificate of Correction		
CORRECTION DATE:	29 Jul 1997		
FILE SEGMENT:	CHEMICAL GRANTED		
ENTRY DATE:	Entered STN: 28 Mar 1997 Last Updated on STN: 6 Nov 1997		

MICROFILM REEL NO: 008118 FRAME NO: 0921
NUMBER OF CLAIMS: 45

PI US 5614178 A 19970325 (CITED IN 027 LATER PATENTS)

ACLM . . . vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs,
anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs,
antipsychotic drugs, antimicrobial drugs, antineoplastic drugs,
antimalarial drugs, muscle relaxant drugs, antispasmodic drugs,
antidiarrheal drugs and bone-active drugs and mixtures thereof.
. . . drug is selected from the group consisting of Beta -lactam drugs,
quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin,
hexamidine isethionate, amikacin, triclosan, doxycycline,
capreomycin, chlorhexidine, chlortetracycline, oxytetracycline,
clindamycin, ethambutol, metronidazole, pentamidine, gentamicin,
kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin,
netilmicin, paromomycin, streptomycin, tobramycin,. . .
. . . vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs,
anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs,
antipsychotic drugs, antimicrobial drugs, antineoplastic drugs,
antimalarial drugs, muscle relaxant drugs, antispasmodic drugs,
antidiarrheal drugs and bone-active drugs and mixtures thereof.

L18 ANSWER 10 OF 14 USPATFULL on STN

ACCESSION NUMBER: 97:70731 USPATFULL

TITLE: Solubility parameter based drug delivery system and
method for altering drug saturation concentration

INVENTOR(S): Miranda, Jesus, Miami, FL, United States
Sablotsky, Steven, Miami, FL, United States

PATENT ASSIGNEE(S): Noven Pharmaceuticals, Inc., Miami, FL, United States

(U.S. corporation)

	NUMBER	KIND	DATE	
	-----	-----	-----	
PATENT INFORMATION:	US 5656286		19970812	<--
APPLICATION INFO.:	US 1994-178558		19940107	(8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-722342, filed on 27 Jun 1991, now patented, Pat. No. US 5474783 which is a continuation-in-part of Ser. No. US 1991-671709, filed on 2 Apr 1991, now patented, Pat. No. US 5300291 which is a continuation-in-part of Ser. No. US 1989-295847, filed on 11 Jan 1989, now patented, Pat. No. US 4994267, issued on 19 Feb 1991 which is a continuation-in-part of Ser. No. US 1988-164482, filed on 4 Mar 1988, now patented, Pat. No. US 4814168, issued on 21 Mar 1989			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Venkat, Jyothsna			
LEGAL REPRESENTATIVE:	Foley & Lardner			
NUMBER OF CLAIMS:	73			
EXEMPLARY CLAIM:	1,4			
NUMBER OF DRAWINGS:	20 Drawing Figure(s); 19 Drawing Page(s)			
LINE COUNT:	3344			
CAS INDEXING IS AVAILABLE FOR THIS PATENT.				

DETD 48. Antimalarial drugs such as Acedapsone, Amodiaquin, Arteether, Artemether, Artemisinin, Artesunate, Bebeerine, Berberine, Chirata, Chlorguanide, Chloroquine, Chlorproguanil, Cinchona, Cinchonidine, Cinchonine, Cycloguanil, Gentiopicrotin, . . .

DETD . . . Iodic Acid, Iodine, Iodine Monochloride, Iodine Trichloride, Iodoform, Methenamine Tetraiodine, Oxychlorosene, Povidone-Iodine, Sodium Hypochlorite, Sodium Iodate, Symclosene, Thymol Iodide, Triclocarban, Triclosan and Troclosene Potassium;

L18 ANSWER 11 OF 14 USPATFULL on STN

ACCESSION NUMBER: 95:78209 USPATFULL

TITLE: Compositions and methods for topical administration of pharmaceutically active agents

INVENTOR(S): Mantelle, Juan A., Miami, FL, United States

PATENT ASSIGNEE(S): Nover Pharmaceuticals, Inc., Miami, FL, United States (U.S. corporation)

	NUMBER	KIND	DATE	
	-----	-----	-----	
PATENT INFORMATION:	US 5446070		19950829	<--
APPLICATION INFO.:	US 1993-112330		19930827	(8)
DISCLAIMER DATE:	20100810			
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-813196, filed on 23 Dec 1991, now patented, Pat. No. US 5234957 which is a continuation-in-part of Ser. No. US 1991-661827, filed on 27 Feb 1991, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Page, Thurman K.			
ASSISTANT EXAMINER:	Azpuru, Carlos			
LEGAL REPRESENTATIVE:	Foley & Lardner			
NUMBER OF CLAIMS:	45			
EXEMPLARY CLAIM:	1			
LINE COUNT:	2434			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD ANTIMALARIAL such as Acedapsone, Alphaaminoquinolines,
4-Aminoquinolines, Amodiaquin, Arteether, Artemether, Artemisinin,
Artesunate, Bebeerine, Berberine, Chirata, Chlorguanide, Chloroquine,
Chlorproguanil, Cinchona, Cinchonidine, Cinchonine, Cycloguanil, . . .
DETD . . . such as Bornyl Chloride, Calcium Iodate, Iodine, Iodine
Monochloride, Iodine Trichloride, Iodoform, Povidone-Iodine, Sodium
Hypochlorite, Sodium Iodate, Symclosene, Thymol Iodide, Triclocarban,
Triclosan, Trocloses Potassium
CLM What is claimed is:
. . . cholinergic blocking drugs, mydriatics, psychic energizers, humoral
agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic
drugs, anti-allergic drugs, decongestants, antipyretics, antimigraine
drugs, antimalarial, antiulcer drugs, peptides, and
anti-estrogens.

L18 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1993:503333 CAPLUS
DOCUMENT NUMBER: 119:103333
ORIGINAL REFERENCE NO.: 119:18441a, 18444a
TITLE: Enhanced skin penetration system for improved topical
delivery of drugs
INVENTOR(S): Deckner, George Endel; Lombardo, Brian Scott
PATENT ASSIGNEE(S): Richardson-Vicks, Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307903	A1	19930429	WO 1992-US8744	19921013 <--
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9228639	A	19930521	AU 1992-28639	19921013 <--
AU 675212	B2	19970130		
EP 608322	A1	19940803	EP 1992-921769	19921013 <--
EP 608322	B1	19980722		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
JP 07500594	T	19950119	JP 1993-507771	19921013 <--
JP 3471354	B2	20031202		
HU 67046	A2	19950130	HU 1994-1106	19921013 <--
BR 9206631	A	19951024	BR 1992-6631	19921013 <--
AT 168563	T	19980815	AT 1992-921769	19921013 <--
ES 2118834	T3	19981001	ES 1992-921769	19921013 <--
CA 2117265	C	20000801	CA 1992-2117265	19921013
CN 1072602	A	19930602	CN 1992-113328	19921016 <--
CN 1050763	C	20000329		
US 6277892	B1	20010821	US 1994-191734	19940204
NO 9401317	A	19940616	NO 1994-1317	19940413 <--
FI 9401770	A	19940415	FI 1994-1770	19940415 <--
HK 1013002	A1	20000623	HK 1998-114300	19981221
PRIORITY APPLN. INFO.:			US 1991-778422	A 19911016
			US 1992-948391	A 19920925

				WO 1992-US8744	A 19921013
				US 1993-59001	B1 19930506

PI	WO 9307903 A1	<u>19930429</u>			
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----

PI	WO 9307903	A1	19930429	WO 1992-US8744	19921013 <--
	W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO,				
	PL, RO, RU, SD				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF,				
	BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
	AU 9228639	A	19930521	AU 1992-28639	19921013 <--
	AU 675212	B2	19970130		
	EP 608322	A1	19940803	EP 1992-921769	19921013 <--
	EP 608322	B1	19980722		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
	JP 07500594	T	19950119	JP 1993-507771	19921013 <--
	JP 3471354	B2	20031202		
	HU 67046	A2	19950130	HU 1994-1106	19921013 <--
	BR 9206631	A	19951024	BR 1992-6631	19921013 <--
	AT 168563	T	19980815	AT 1992-921769	19921013 <--
	ES 2118834	T3	19981001	ES 1992-921769	19921013 <--
	CA 2117265	C	20000801	CA 1992-2117265	19921013
	CN 1072602	A	19930602	CN 1992-113328	19921016 <--
	CN 1050763	C	20000329		
	US 6277892	B1	20010821	US 1994-191734	19940204
	NO 9401317	A	19940616	NO 1994-1317	19940413 <--
	FI 9401770	A	19940415	FI 1994-1770	19940415 <--
	HK 1013002	A1	20000623	HK 1998-114300	19981221

IT	Anesthetics
	Anti-infective agents
	Antiarrhythmics
	Antidepressants
	Antiemetics
	Antihistaminics
	Antihypertensives
	<u>Antimalarials</u>
	Antitussives
	Appetite depressants
	Cardiotonics
	Cholinergic agonists
	Diuretics
	Hypnotics and Sedatives
	Inflammation inhibitors
	Muscle relaxants
	Neoplasm inhibitors
	Nervous system stimulants
	Sunscreens
	Tranquilizers and Neuroleptics
	Ulcer inhibitors
	Vasoconstrictors
	Vasodilators
	Wound healing promoters
	(topical compns. containing dialkylaminoalkyl acrylate polymers and)

IT	55-56-1, Chlorhexidine	57-62-5, Chlortetracycline	57-92-1,
	Streptomycin, biological studies	59-01-8, Kanamycin	74-55-5,
	Ethambutol	79-57-2, Oxytetracycline	100-33-4, Pentamidine
	biological studies	154-21-2	443-48-1, Metronidazole
			564-25-0
	768-94-5, Tricyclo[3.3.1.1 ^{3,7}]decan-1-amine	914-00-1, Methacycline	
	1403-66-3, Gentamicin	1404-04-2, Neomycin	3380-34-5,
	<u>Triclosan</u>	7542-37-2, Paromomycin	10118-90-8, Minocycline

09763499

11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin
37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin
85721-33-1, Ciprofloxacin
RL: BIOL (Biological study)
(antimicrobial topical compns. containing dialkylaminoalkyl acrylate
polymers and)

L18 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1993:503334 CAPLUS
DOCUMENT NUMBER: 119:103334
ORIGINAL REFERENCE NO.: 119:18441a,18444a
TITLE: Enhanced skin penetration system for improved topical
delivery of drugs
INVENTOR(S): Deckner, George Endel; Lombardo, Brian Scott
PATENT ASSIGNEE(S): Richardson-Vicks, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307902	A1	19930429	WO 1992-US8741	19921013 <--
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9228064	A	19930521	AU 1992-28064	19921013 <--
AU 675211	B2	19970130		
EP 608320	A1	19940803	EP 1992-921755	19921013 <--
EP 608320	B1	19980128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
HU 74560	A2	19970128	HU 1994-1107	19921013 <--
AT 162725	T	19980215	AT 1992-921755	19921013 <--
ES 2114569	T3	19980601	ES 1992-921755	19921013 <--
CN 1072863	A	19930609	CN 1992-112390	19921016 <--
IN 178157	A1	19970308	IN 1992-DE1011	19921105 <--
IN 181010	A1	19980411	IN 1992-DE1013	19921105 <--
NO 9401319	A	19940616	NO 1994-1319	19940413 <--
FI 9401771	A	19940415	FI 1994-1771	19940415 <--
US 5756118	A	19980526	US 1995-462258	19950605 <--
US 5756119	A	19980526	US 1995-462376	19950605 <--
US 5773023	A	19980630	US 1995-462710	19950605 <--
US 5780049	A	19980714	US 1995-464991	19950605 <--
US 5776485	A	19980707	US 1995-469701	19950606 <--
US 5874095	A	19990223	US 1998-49367	19980327
PRIORITY APPLN. INFO.:			US 1991-778424	A 19911016
			US 1992-957752	B1 19921002
			WO 1992-US8741	A 19921013
			US 1993-111032	B1 19930824
			US 1994-228167	B1 19940415
			US 1995-390902	B3 19950216
			US 1995-462710	B3 19950605
PI WO 9307902 A1 19930429				
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307902	A1	19930429	WO 1992-US8741	19921013 <--
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO,				

Jagoe

PL, RO, RU, SD
 RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF,
 BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG

AU 9228064	A	19930521	AU 1992-28064	19921013 <--
AU 675211	B2	19970130		
EP 608320	A1	19940803	EP 1992-921755	19921013 <--
EP 608320	B1	19980128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
HU 74560	A2	19970128	HU 1994-1107	19921013 <--
AT 162725	T	19980215	AT 1992-921755	19921013 <--
ES 2114569	T3	19980601	ES 1992-921755	19921013 <--
CN 1072863	A	19930609	CN 1992-112390	19921016 <--
IN 178157	A1	19970308	IN 1992-DE1011	19921105 <--
IN 181010	A1	19980411	IN 1992-DE1013	19921105 <--
NO 9401319	A	19940616	NO 1994-1319	19940413 <--
FI 9401771	A	19940415	FI 1994-1771	19940415 <--
US 5756118	A	19980526	US 1995-462258	19950605 <--
US 5756119	A	19980526	US 1995-462376	19950605 <--
US 5773023	A	19980630	US 1995-462710	19950605 <--
US 5780049	A	19980714	US 1995-464991	19950605 <--
US 5776485	A	19980707	US 1995-469701	19950606 <--
US 5874095	A	19990223	US 1998-49367	19980327

IT Anesthetics
 Anti-infective agents
 Antiarrhythmics
 Antidepressants
 Antiemetics
 Antihistaminics
 Antihypertensives
Antimalarials
 Antitussives
 Appetite depressants
 Cardiotonics
 Cholinergic agonists
 Diuretics
 Hypnotics and Sedatives
 Inflammation inhibitors
 Muscle relaxants
 Neoplasm inhibitors
 Nervous system stimulants
 Sunscreens
 Tranquilizers and Neuroleptics
 Ulcer inhibitors
 Vasoconstrictors
 Vasodilators
 Wound healing promoters
 (topical compns. containing polyacrylamide and)

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1,
 Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5,
 Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0,
 biological studies 154-21-2 443-48-1, Metronidazole 564-25-0
 768-94-5, Tricyclo[3.3.1.1^{3,7}]decan-1-amine 914-00-1, Methacycline
 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5,
Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline
 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin
 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin
 85721-33-1, Ciprofloxacin
 RL: BIOL (Biological study)
 (antimicrobial topical compns. containing polyacrylamide and)

L18 ANSWER 14 OF 14 USPATFULL on STN

ACCESSION NUMBER: 93:26884 USPATFULL
 TITLE: Oral osmotic device
 INVENTOR(S): Edgren, David E., El Granada, CA, United States
 Bhatti, Gurdish K., Fremont, CA, United States
 PATENT ASSIGNEE(S): ALZA Corporation, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5200194		19930406 <--
APPLICATION INFO.:	US 1991-809741		19911218 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Horne, Leon R.		
LEGAL REPRESENTATIVE:	Duvall, Jean M., Miller, D. Byron, Stone, Steven F.		
NUMBER OF CLAIMS:	19		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 1 Drawing Page(s)		
LINE COUNT:	880		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . (LISTERINE sold by Warner-Lambert Co. of Morris Plains, N.J.); benzophenathradine (VIADENT sold by Vipont Pharmaceutical, Inc. of Fort Collins, Colo.); triclosan and zinc citrate; stannous fluoride; and cetylpyridinium chloride (CEPACOL sold by Marion Merrell Dow of Cincinnati, Ohio and SCOPE sold. . .

DETD . . . sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory drugs, local anesthetics, muscle contractants, anti-plaque agents, anti-microbials, anti-fungals, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents, and cardiovascular drugs.

DETD . . . alkaloids such as sanguinarine and sanguinarine chloride, metal salts such as zinc citrate, non-charged phenolic agents such as thymol and triclosan, enzyme systems such as mutanases, amylogycosidase and glucose-oxidase, sugar substitutes such as xylitol and mannitol, fluorides such as stannous fluoride. . .

CLM What is claimed is:

. . . benzalkonium chloride, aminacridine hydrochloride, mepacrine hydrochloride, hydrogen peroxide, potassium peroxidiphosphate, proguanil hydrochloride, dibromopropamide diisothionate, hexidine, alexidine, octenidine, zinc citrate, thymol, triclosan, mutanases, amylogycosidase, glucose-oxidase, xylitol, mannitol, stannous fluoride, sodium fluoride, decapinol, sodium polyvinylphosphonic acid, perfluoroalkyl surfactants and cetyltrimethylbenzyl ammonium chloride.

CLM What is claimed is:

. . . benzalkonium chloride, aminacridine hydrochloride, mepacrine hydrochloride, hydrogen peroxide, potassium peroxidiphosphate, proguanil hydrochloride, dibromopropamide diisothionate, hexidine, alexidine, octenidine, zinc citrate, thymol, triclosan, mutanases, amylogycosidase, glucose-oxidase, xylitol, mannitol, stannous fluoride, sodium fluoride, decapinol, sodium polyvinylphosphonic acid, perfluoroalkyl surfactants and cetyltrimethylbenzyl ammonium chloride.

IT 54-21-7, Sodium salicylate 56-95-1, Chlorhexidine diacetate 64-17-5,
 Ethanol, biological studies 69-05-6, Mepacrine hydrochloride 69-65-8,

09763499

Mannitol 87-99-0, Xylitol 89-83-8, Thymol 122-18-9,
Cetyldimethylbenzylammonium chloride 123-03-5, Cetylpyridinium chloride
134-50-9 522-51-0, Dequalinium chloride 532-32-1, Sodium benzoate
546-46-3, Zinc citrate 614-87-9 637-32-1, Proguanil hydrochloride
1330-43-4, Boron sodium oxide (B4Na2O7) 2447-54-3, Sanguinarine
3380-34-5, Triclosan 3697-42-5 5578-73-4, Sanguinarine
chloride 7681-49-4, Sodium fluoride, biological studies 7722-84-1,
Hydrogen peroxide, biological studies 7783-47-3, Stannous fluoride
9001-37-0, Glucose oxidase 9032-08-0 9075-84-7, Mutanase 15593-49-4
18472-51-0, Hexidine 22573-93-9, Alexidine 60406-21-5 62571-86-2
71251-02-0, Octenidine 79874-76-3, Decapinol
(therapeutic oral osmotic device containing)